

STUDIES ON ERYTHROID
ELEMENTS AND SERUM IRON
IN NORMAL PREGNANCY

By

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From the Clinic of Obstetrics and Gynecology of the University of Uppsala.
Chief: Professor John Naeslund.

Studies on Erythroid Elements and Serum Iron in Normal Pregnancy.

By

PER LUNDSTRÖM.

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Preface.

A glance at the literature shows that the problem of blood changes in pregnancy is still far from its solution. The purpose of the present work is to try to give a more definite idea of the changes during pregnancy in hemoglobin, red blood cells, hematocrit, corpuscular values,

and serum iron. The effect of iron therapy was gone into at the same time. The investigation was commenced in 1946.

The cases were collected at the Clinic of Obstetrics and Gynecology of the University of Uppsala. The Chief of the Clinic, Professor John Naeslund, suggested the problem to me. He has been very helpful and therefore I wish to thank him very warmly. Thanks to him I received the help I needed for the investigation, and he also gave me good advice during the planning of the investigation.

When analyzing the material from a statistical point of view I had the great advantage of discussing the problems with Professor Gunnar Dahlberg. He has taken great interest in my work and afforded me the opportunity of considering it in its wider aspects. I am most indebted to him.

Professor Erik Ask-Upmark, Professor Gunnar Blix, and Professor Jan Waldenström have devoted much time to discussing vital problems with me. I am most grateful to them for their stimulating interest and good advice.

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I wish to record my deep appreciation of the never failing sense of duty, application and resourcefulness shown by Nurse Ingegerd Lundin in assisting me in my work. I also wish to thank Nurse Valborg Arvidsson who ably executed part of the determinations (in the iron-treated material).

Several members of the Staff at the Clinic for Women's Diseases at Uppsala have assisted me in various ways, and for this I thank them warmly.

My wife has helped me with the statistical computations, and I am very grateful to her.

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Uppsala, November 1949.

Per Lundström.

CHAPTER I.

Review of Literature.

Erythroid Elements and Hematocrit in Pregnancy and Post Partum.

These studies were either carried out by testing the same person throughout pregnancy and post partum or by testing different persons at various stages. Often a compromise has been made between these two methods.

Table 1 briefly summarizes data from authors who have used the former method, and table 2 gives the results obtained by the second procedure. On the whole, the results are similar, and that is what could be expected.

The tables require some comment. In some cases the technique has been described, and the determinations have been made with the aid of calibrated apparatus. Data as to the error of method is almost always missing and this quantity is of decisive importance in hematologic investigations. Often, moreover, the authors have no normal material. The personal factor often plays an important part, especially in hemoglobin determinations (see Chapter 2), and therefore it is probably doubtful that the hemoglobin value is an absolute figure. ENGHOF (1937), besides, has emphasized the importance of counting the red cells by means of a satisfactory method. ADAIR, DIECKMANN, and GRANT (1936) have stated that the error of method in counting red corpuscles with the technique used in the clinic laboratory amounted to 13.7 per cent. Probably the error may be even larger if standardized apparatus is not employed.

One of the first investigations of the changes of the hematocrit level in pregnancy with satisfactory technique, was made in 1920 by GRAM. The number of cases in the several months of pregnancy is small, however, and Gram did not base his conclusions on statistical analyses.

KÜHNEL (1925) had a satisfactory technique with low errors of method. His report contains data on the changes in the blood during and after pregnancy and up to about one year after delivery. In a very laudable manner he critically summarized earlier literature, emphasizing that, often because of obsolete, undescribed techniques with unknown errors and mostly small and inadequately substantiated materials, it is not possible to obtain a sound conception of the changes affecting the red blood corpuscles during pregnancy.

Even in the first stages of pregnancy, Kühnel found that the hemoglobin content and the erythrocyte and hematocrit counts decreased uniformly. The decrease continued to the 16th—20th week of pregnancy, at which time the means were 10—15 per cent lower than in the normal material. In 34th week there was a significant increase by 6—8 per cent. After the 34th week, the values for red cells and

Table 1. *Variations of blood values according to authors who have tested the same person throughout pregnancy and puerperium.*

Hematocrit according to Wintrobe = (a); Hematocrit according to van Allen = (b); Hematocrit according to Enghoff = (i); Low error of methods = (c); Calibrated pipettes and chamber = (d); Duplicate determinations = (e); Mean corpuscular diameter according to Price-Jones = (f); Standard methods = (g); Oxygen capacity = (h); Mean corpuscular average thickness = M.C.A.Th.; Autenrieth = A-rieth; Haldane = Ha; Hayden-Hauser = H.-H.; Hellige = Hel.; Newcomber = Newc.; Hemoglobin = Hb.; Red corpuscles = R.B.C.; Hematocrit = H-t; month or week of pregnancy = mo. or w.; post partum = p.p.; Pregnancy = P.; Trimester = T.

Author	Year	Method	No.	Normal material	Findings
Kühnel	1925	Sahli Bürker-Türk H-t 3000 revs. (c)	15	10	Uniform decrease during P. by 10—15 per cent. Chloro-anemia at term. Increase within a w. Normal not until half a year. During this time some microcytosis.
Galloway	1929	Sahli	382	—	Progressive anemia as pregnancy advances and a more marked reduction of Hb. than of R.B.C.
Skajaa	1929	H-t 2500 revs. (c)	120	10 (44.4 vol. %)	36.4 at term. Normal values 2 w. p.p. In 34 cases without complications.
Bland et al.	1930	—	100	—	No increase for R.B.C. in last T.
Adamson Smith	1932	Sahli	116	—	Decrease of Hb and R.B.C. by 10.5 per cent during 2nd T. Unchanged in 3rd T. R.B.C. decreases but less than Hb. Normal figures (80 per cent Hb., and 4.6 mill. R.B.C.) 2 w. p.p.
Strauss and Castle	1932	Sahli (d)	20	—	Anemia in 3rd T., but only in patients with deficient diet and gastric anacidity. 9 in the optimal group lost 5 per cent Hb. from 3rd mo. during P. to 10 days p.p.
Davies and Shelley	1934	—	51	—	Decrease of Hb. and R.B.C. of normal women during P. not significant.
Davis and Walker	1934	H.-H.	69	—	Anemia increases as gestation progresses. Slight increase of the blood values p.p. but 6 w. p.p. the incidence of anemia is increased.
Dieckmann and Wegner	1934	Palmer (d) (c)	15 +	—	Max. Hb. decrease at 26—35 w. of P. by 15 per cent. H-t similar, but more rapid recovery p.p.; 8 w. p.p. still below normal. R.B.C. similar; normal count 3 w. p.p. Marked variation of all indices with slight increase of M.C.V. at 26—35 w. of P. and p.p. Slight increase of corpuscular Hb. in per cent and amount during the greater part of P., but normal at term and during puerperium.
Jerlov	1934	A.-rieth	145	—	Decrease of Hb. during P. No increase the last 3 mo.

(Table 1 continued.)

Author	Year	Method	No.	Normal material	Findings
Richter et al.	1934	Sahli	61	—	Progressive reduction in Hb. and R.B.C., greater decrease for Hb. proportionally (11 per cent from 3rd m. to 2 w. before term). Rapid increase p.p., gradual drops to minimum 6 w. p.p., then a gradual rise.
Boycott	1936	Ha	152	—	Hb. decreases 13 per cent from 4th mo. to 9th mo. then slight increase.
Feldman et al.	1936	Newc. Leitz (a)	20 +	—	Max. reduction of blood solids and Hb. at 220th day of P. Pronounced rise to 45 days p.p.
Thompson et al.	1938	Sahli (d) (e)	14	28	Lower Hb. and R.B.C. and H-t during P., then normal. In 10th mo. a return toward normal begins which continues on through puerperium.
Watson	1938	Sahli (d)	40	—	Increase of Hb. during P. from the 4th mo.; practically normal 10 days p.p. 6—9 mo. p.p. normal value but decreased M.C.V.; M.C.H. and M.C.H.C. within normal range during P.
Bethell et al.	1939	Sahli	133	100	Decrease of blood values, most for Hb. in 30 »healthy women»; minimum in 6th mo., thereafter increase. 42 days p.p. normal values, except Hb.
Gottlieb and Strean	1939	—	275	—	Continued decrease of Hb. and R.B.C. during P. Hb. decreases more than R.B.C. The decrease can be prevented through iron. Normal values in iron treated cases 6 w. p.p.
Labate	1940	Sahli (a)	19	—	Increase of Hb, R.B.C. and H-t during last 2 w. during P., R.B.C. and H-t normal 10 days p.p., but Hb. 9 per cent less than normal. M.C.V. and M.C.H. unchanged, M.C.H.C. subnormal.
Botella-Llusia and Arranz	1941	—	20	20	At term H-t = 29.2, M.C.V. = 80.1. During latter part of labour H-t = 33.7, M.C.V. = 80. During 3 first days p.p. H-t = 26.5, M.C.V. = 96. 3rd—7th days p.p. H-t = 34.3, M.C.V. = 96.
Hamilton and Wright	1942	Ha	392	—	Hb. decreases 12 per cent without iron treatment from 3rd to 5th mo. term (196 cases).
Merchante	1942	—	46	—	Hb. decrease by 9 per cent from 1st mo. to 9th mo. R.B.C. decrease by 18 per cent from 1st mo. to 9th mo. H-t decrease by 8 per cent from 1st mo. to 9th mo.
Peralta-Ramos and Gascon	1942	—	1012	—	Decrease of R.B.C. and Hb. Lowest in 9th mo. of P. The rate of decline of Hb. slowed in the last T.
Evans	1943	Sahli-Adams	117	—	Decrease of Hb. and R.B.C. most of Hb. At first examination only 4 per cent < 10 gm. Hb. In 6th mo. to 8th mo. 87 per cent < 10 gm. Hb.

(Table 1 continued.)

Author	Year	Method	No.	Normal material	Findings
Elliott	1944	Ha (a) (f)	48	—	Increase of variability of mean corpuscular diameter particularly in the cases of anemia (see table 3). Increase of mean corpuscular fragility during P., decrease immediately p.p. Tendency to decrease of M.C.A.Th. in anemia in P.
Wolff and Limarzi	1945	—	30	—	Decrease of Hb., R.B.C. and H-t during P. M.C.V. unchanged. M.C.H.C. at lower limit for normality. Normal levels 6 w. p.p.
Hamilton and Higgins	1949	H.-H. (g)	411	—	Nearly identical values of Hb., R.B.C. and H-t and serum protein during P. Lowest values in 6th mo. 8 w. p.p. higher values than in 3rd mo. during P.
Naeslund	1949	(i) (c)	49	—	Statistically significant decrease of H-t 4-8 hours p.p. (also for hemorrhage group < 300 cc). 3 days p.p. significant increase of H-t and at 7th day p.p. of R.B.C. too.

hematocrit remained practically unchanged but the hemoglobin returned to the previous minimum value. Kühnel suggested that pregnancy is associated with "mild chloro-anemia". After delivery, the blood values at first decreased in proportion to the intrapartum hemorrhage but then they increased steadily in the first week of the puerperium. Thereafter, the different blood values returned to normal at different rates, the hemoglobin only after about 6 months. Meanwhile the mean corpuscular volume was subnormal.

One of the most quoted papers is that published by DIECKMANN and WEGNER in 1934. These authors followed 15 cases in pregnancy and the puerperium with a number of different blood analyses. They also had a material that was examined before delivery and repeatedly up to 8 weeks post partum. Their report is very comprehensive and it is impossible here to discuss it in detail. I shall, however, comment on some items.

It would have been desirable if the authors had described their statistical methods. For example, the standard error of the mean does not seem to have been computed in the ordinary manner with the aid of the standard deviation and the number of cases. They stated that at the end of pregnancy the hemoglobin value increases slightly and at certain times they found a slight increase of the mean corpuscular volume (see table 1). These statements cannot be confirmed by the data in their tables — the differences seem to be statistically random. Their statement that "...there are marked changes in the erythrocytes in pregnancy, suggestive of a beginning primary anemia" must be con-

Table 2. *The variation of blood values according to authors who have tested different persons at various stages during pregnancy and puerperium.*

(Abbreviations see table 1.)

Author	Year	Method	No.	Normal material	Findings
Gram	1920	H-t	59	40 (40 vol. %)	32 vol. % in 5th mo., 38 vol. % in 10th mo. «Physiological anemia» during P.
Jerlov	1929	A-rieth	1143	—	Hb. decrease from 3rd mo. to 10th mo. by 14 per cent.
Strauss and Castle	1932	Sahli	200	—	Same results as in table 1.
Schultz	1933	Sahli	349	—	Hb. during pregnancy 10 per cent lower than normal. No increase at term.
Oberst and Plass	1936	(h)	20	10	Decrease during P. Increase to supernormal values in some cases early during labour. M.C.H.C. at a high level during P. and labour. Then decrease.
Watson	1938	See table 1	500	—	Rapid rise of Hb. p.p.
Pitts and Packham	1939	Haskins-Sahli (d), (e)	407	24	Hb. and R.B.C. during P. 10—15 per cent lower than normal.
Harjola	1946	Sahli Türk-Leitz (b)	60	16	Slight decrease of Hb., R.B.C. and H-t, lying 2.3, 5.5 and 4.1 per cent lower than normal, respectively. (The cases had been chosen so that Hb. > 70 per cent Sahli) M.C.V. about 89 c.μ, saturation index average 0.98.
Macarthur	1948	H-t	600	—	In 3rd T. minimum value, about 80 per cent of normal mean.

sidered with reserve since their data do not seem to fit their conclusions. The slight hemoglobin increase at the end of pregnancy seems to be statistically random, but Dieckmann has later used it on several occasions as an argument against the efficacy of iron treatment in pregnancy.

From tables 1 and 2 it will be seen that the blood values decrease during pregnancy. (DAVIES and SHELLEY, however, did not consider the changes significant.) Often the authors report an increase at the end of pregnancy (GRAM, KÜHNEL, DIECKMANN and WEGNER, BOYCOTT, FELDMAN *et al.*, THOMPSON *et al.*, BETHELL *et al.*, LABATE), whereas other authors have either found the lowest values in the last trimester or have been unable to observe any increase at all toward the end of pregnancy. WATSON reports an hemoglobin increase as from the 4th month of pregnancy.

After delivery, some authors have found a return to normal blood

values within 6 weeks post partum (SKAJAA, ADAMSON and SMITH, OBERST and PLASS, WATSON, WOLFF and LIMARZI) while others have found that the different blood values return to their normal levels at unequal rates. As already mentioned, Kühnel has emphasized the long time that elapses post partum before hemoglobin attains normal values. Some authors even report a higher frequency of anemia 6 weeks after delivery (DAVIS and WALKER, RICHTER *et al.*).

The changes of the corpuscular values and different indices during pregnancy has evidently not been studied as much as the variation of hemoglobin, red cells and hematocrit. On the whole, however, it appears that the colour index decreases in pregnancy, and it is uncertain if this depends on reduced hemoglobin saturation or on reduced mean corpuscular volume or on both. Only BOTELLA-LLUSIA and ARRANZ have reported a reduced mean corpuscular volume in healthy pregnant women, while Dieckmann and Wegner report a slight increase during some periods. The mean corpuscular hemoglobin concentration according to Oberst and Plass lies on a higher level during pregnancy, whereas Wolff and Limarzi express the opinion that there is a tendency to decrease. According to Botella-Llusia and Arranz the mean corpuscular volume increases after delivery but Kühnel and Watson report that several months post partum this blood characteristic is decreased.

Serum Iron in Pregnancy and Post Partum.

Serum iron is a transport iron. The serum iron level is a function of several, partly unknown factors. Probably it reflects the balance between absorption and function (MOORE *et al.* 1937), but other factors also probably play their part, e. g. endocrinous influences (VAHLQUIST 1941). In 1946 WALDENSTRÖM stated: "It is thus possible that a chronically low level of the serum iron is not an indicator of empty iron depots but rather a sign of dysregulation." He assumes that the liver function and some nutritional factors as well as hereditary causes may be of importance. It is most difficult, therefore, to draw conclusions from the serum iron level as to the content of iron in the organism; a supposed deficiency may for example very well be of functional origin.

Only few studies have been carried out as regards the changes of the serum iron during and after pregnancy as compared with those dealing with the erythroid elements.

HEILMEYER and PLÖTNER (1937), using their own satisfactory method, found (16 cases) in the 9th month of pregnancy a mean of 99.5 γ per cent, range 32—190. They assumed that the low values may be a sign of a preanemic stage. The normal value was 89 γ per cent.

In 1938 NEUWEILER examined 17 cases about 2 hours before parturition. The mean of serum iron value was 92.7 γ per 100 cc. 2 hours

post partum the mean had dropped to 75.3 γ per cent. The mean content in the retroplacental blood was 107.1 γ per cent. In 1942 the same author found a difference of 15 γ per cent between the mean serum iron value in a normal material consisting of 31 cases on one hand and 81 women in the end of pregnancy on the other. He also found that post partum serum iron drops rapidly irrespective of the antepartum value. In the days after delivery the serum iron level is not with certainty influenced by the size of the intrapartum hemorrhage. However, there is always an increase after the first 24 hours following parturition. Women given iron before delivery usually post partum show a higher serum iron value than untreated women. The number of cases in the different groups after parturition is small and Neuweiler puts the error of method at ± 30 per cent. Therefore his results from changes taking place post partum would seem to be uncertain.

Van Goidsenhoven *et al.* (1938) found the mean serum iron value, on the basis of 10 determinations during the latter stages of pregnancy, to be 99.6 γ per cent and thus lower than in their 10 normal cases (118 γ per cent).

GUGGISBERG (1941) found a serum iron variability of 50—151 γ per cent during pregnancy, and he attributed the cases with high values to increased requirements of iron during pregnancy. The low values, on the other hand, he assumed to be due to inadequate adjustment to the increased iron requirements.

In 1941 VAHLQUIST studied 30 cases immediately after delivery. The mean serum iron value was 58.9 ± 4.8 γ per cent and consequently much lower than the mean for the normal material which was 123.0 ± 4.5 γ per cent. In some cases he found fairly high values during pregnancy and he assumed that in the early months of pregnancy the serum iron value is perhaps higher than normal.

In 1941 ALBERS presented a comprehensive monograph entitled "Eisen bei Mutter und Kind." His material is not treated statistically. In his different series the negligible variability is striking. In 39 normal cases the standard deviation is 14.3 ± 1.62 , which is less than in other comparable materials and in a group of 25 women during delivery the standard deviation is 9.6. (These standard deviations are calculated by me.) The author does not mention how the material was selected but the negligible variation might possibly be looked for here.

In 50 healthy pregnant women, most of them in the 9th and 10th month, Albers found a mean of 124 γ per cent. The variation between different periods of pregnancy was negligible. During delivery the mean increased to 133 γ per cent, but immediately after parturition it dropped by 24 per cent to 101 γ per cent. In the puerperium the mean serum iron value lay practically constant at or slightly above 80 γ per cent for hemorrhages up to 250 cc but it was lower for greater hemorrhages. In so called iron deficiency anemia the serum iron value was low.

Moreover, Albers found differences during pregnancy between various ages. So, for example, one group of 6 cases older than 30 years lay 9 γ per cent lower than the younger groups, but the mean error of the difference is 7.1 γ per cent and therefore the difference may be due to random variation. He also found differences between groups with different numbers of deliveries (max. diff. 10 γ per cent) but these differences, too, are random.

BROCKNER-MORTENSEN (1942) often found low serum iron values during pregnancy.

In 1942 SUNDELIN examined 135 healthy pregnant women in 6 groups of which 5 represented each of the 5 last months of pregnancy. During the first of these months he found "normal" serum iron values (average 118 γ per cent) and then a decrease to about 48 γ per cent in the 8th—9th month and an increase to 80 γ per cent in the 10th month. He states that the marked reduction may partly be due to latent sideropenia that in turn may give rise to "deep" anemic conditions. The increase in the 10th month would then depend on "inspissation" of the blood. The author had no normal material of his own. The explanation of the increase in the 10th month is difficult to apprehend, since simultaneous determinations of red cell count and hemoglobin did not increase correspondingly.

In RENAER'S (1942) 13 cases the ante partum mean was 98.5 γ per cent and 3 hours post partum it was 69.6 γ per cent. Of DAHL'S (1945) 48 cases 43 had less than 70 γ per cent in the latter half of pregnancy while 24 out of 50 puerperal women had less than 70 γ per cent.

In 1946 HEMMELER stated that low serum iron values are not uncommon at the end of pregnancy.

In that part HARJOLA'S (1946) material of gravidae where Sahli was in excess of 70 per cent, the serum iron value remained largely unchanged during the several months of pregnancy. In these 54 cases the mean was 114 ± 5.1 γ per cent. Harjola states that these values were higher than in the normal material. (Since the mean in the normal material was 95 ± 6.7 γ per cent; the difference, however, is not significant. $P > 0.02$.) In gravidae with hemoglobin 60—69 per cent Sahli the mean of 40 serum iron determinations was 73 γ per cent and in 30 determinations with hemoglobin < 60 per cent Sahli the mean was 54 γ per cent.

LAURELL (1947) found the same type of changes as Sundelin (51 pregnant cases). He examined 17 women immediately after parturition, the mean being 80 γ per cent. The normal mean value was 108 γ per cent in his material of 39 healthy non-pregnant women.

SUMMARY. — During pregnancy hemoglobin, red cell and hematocrit decrease. Their varying relationships and behaviour after parturition are not fully known. According to some authors the blood values return to a normal level already at term or during labour, or very soon

after delivery (see tables 1 and 2). Others maintain that the return is slow and unequal in length for the different blood values.

It seems probable that the serum iron level at the beginning of pregnancy is normal or even greater than normal compared with the non-gravid standard, and that it definitely is decreased at the end of pregnancy. Soon after delivery the serum iron value seems to drop still more only to increase slightly during the puerperium. When the value returns to normal level is not clear.

EVANS (1943) puts it this way (he does not refer to serum iron, however) "The entire picture of blood changes in pregnancy is still confusing."

*

The Plasma Volume and Iron Requirements in Pregnancy.

The variation affecting the erythroid elements and serum iron during pregnancy and post partum has generally been explained as follows: partly the plasma volume is said to increase in pregnancy, resulting in dilution and consequently lowering of the blood characteristics; partly the growing fetus as well as the growth of uterus and placenta require iron. This iron must be supplied by the mother and under unfavourable conditions iron deficiency with secondary anemia might therefore arise in the mother. A few authors, among them Kühnel (1925), PERALTA-RAMOS and GASCON (1942), have assumed that the reason for low blood values during pregnancy is increased destruction of blood. However, to my knowledge the literature contains no certain proofs of such an assumption. The question is briefly discussed in Chapter 5.

A. The Plasma Volume in Pregnancy.

An increase of the blood volume has been found by several investigators. They have as a rule estimated the total plasma volume by means of a suitable dye and then calculated the total volume of blood with the aid of the plasma volume and the hematocrit value.

However, the method of estimating the plasma volume has mostly been unsatisfactory, and the calculation of the total blood volume in the above manner suffers from grave errors (GIBSON and EVANS 1937, STEAD and EBERT 1941, HAHN *et al.* 1942).

KEITH, ROWNTREE and GERAGHTY (1915), KABOTH (1923), BOHNEN and BORRMAN (1925), HNÁTEK (1927), DIECKMANN and WEGNER (1934), RICHTER *et al.* (1934), BETHELL (1936), ALBERS (1939), using the above method (sometimes slightly modified), found an increase of the plasma volume in pregnancy, the increase usually being largest at the end.

The plasma volume as a rule returned to a normal level within one week after delivery.

THOMPSON *et al.* (1938) adopted the modifications introduced by Gibson and Evans for the estimation of the plasma volume. They found in 14 pregnant women (altogether 36 observations in different periods) a successive increase of the plasma quantity with a maximum of 165 per cent of normal in the 9th month. In the 10th month the value dropped slightly and lay but 50 per cent higher than in the 28 normal cases. 2 weeks post partum the plasma quantity had returned to normal.

WERKÖ *et al.* (1948) and unpublished results by BUCHT (1949) on the basis of a large material confirm the increase of the total plasma volume during pregnancy, the maximum being attained in the 9th month. No significant differences have appeared between the 9th and 10th months.

The increase of the plasma volume in pregnancy has generally been interpreted as hydremia. The problem has been approached in several ways, such as by estimating the moisture content, specific gravity, total proteins and freezing point.

In the nineteenth century, NASSE several times described his studies of the specific gravity of plasma and whole blood during pregnancy. In whole blood he found a marked decrease which was greatest in the 6th—8th month (23 cases averaging 1.0497 as against 1.0553 in non-pregnant women). In the 9th month the figure was 1.0513 ($n = 23$) and during delivery 1.0533 ($n = 10$). The specific gravity of serum changed negligibly in the last 3 months of pregnancy but it was lower than in non-pregnant women. During delivery the specific gravity becomes normal. Stander and Taylor (1920) found that the moisture content increases up to the 7th month.

POLOWE'S study of 1932 yielded findings similar to the ones described above. In 1936 OBERST and PLASS (small number of cases in the several groups) showed how the moisture content in plasma and whole blood rises during pregnancy while the specific gravity falls. When the moisture content in plasma increases the amount of plasma proteins decreases. The reduction of the hematocrit and hemoglobin values and the specific gravity agree with the decrease in plasma proteins. The authors considered that this indicates a simple dilution of the plasma. According to the authors the above characteristics return to normal at the beginning of labour. They assumed that this means that pregnancy does not give rise to anemia. MULL (1945) was of a like opinion and emphasized that the reason might be one of hormonal changes during pregnancy.

The reduction of total proteins in plasma and serum during pregnancy, usually with a rapid return to normal post partum, has also been shown by among others PLASS and BOGART (1924), PLASS and MATTHEWS (1926), DIECKMANN and WEGNER (1934), FELDMAN *et al.* (1936),

LABATE (1940), MACARTHUR (1948) and HAMILTON and HIGGINS (1949) and others. TOVERUD (1935), however, in 79 cases during pregnancy found only 2 cases of reduced protein concentration. PERALTA-RAMOS and GASCON (1942), by means of freezing point and protein determinations, were unable to confirm hemodilution.

B. Iron Requirements during Pregnancy.

1. *Fetal Iron Requirements.* HUGOUNENQ (1889) found that a mature fetus contains 295 mg of iron but CAMERER and SÖLDNER (1900, 1903) obtained a higher value. In their 6 cases they used two different methods of determining the iron content. Their mean figure is 365 mg and 440 mg respectively. JERLOW (1934) found that the mature fetal body contains 335 mg of iron, SWANSON and IOB (1939) obtained the figure 284 mg. As the concentration of iron in the fetus roughly corresponds to its weight (actually to the weight of solids, Hugounenq 1900 and Swanson and Iob 1938) the fetus during the last 3 months of fetal life takes up about $\frac{2}{3}$ of its iron requirements. The same result in principle was arrived at by MACY and HUNSCHER (1934) and TOVERUD (1935).

2. *Total Iron Requirements During Pregnancy.* This amount has been estimated rather differently. COONS (1932) assumed that during pregnancy the total iron requirements were 900 mg, while Macy and Hunscher estimated it to be 750 mg. HEATH and PATEK (1937) thought that 600 mg was enough. FULLERTON (1936) made a critical survey of the requirements on the basis of previous reports. If the iron loss due to the intrapartum hemorrhage and lactation is taken into account, Fullerton estimated a total requirement of 905 mg during pregnancy and puerperium.

In connection with the requirement of iron during pregnancy it may be of interest to discuss the question of menstrual iron losses. BARER, FOWLER and BALDRIDGE (1935) found that in 50 cases the loss varied between 3.8 and 78.4 mg of iron per menstrual period. In 1936 BARER and FOWLER studied 100 women and found a mean loss of 19.5 mg. LEVERTON and ROBERTS (1937), SCOTT (1938) and LUNDHOLM (1939) obtained values ranging between 11 and 23 mg. When the menstrual hemorrhages are considerable, the loss of iron may be much larger (Barer and Fowler).

SUMMARY. — The plasma volume increases markedly throughout the course of pregnancy, according to Thompson *et al.* up to 65 per cent above the normal value and it probably in part explains the decrease in the erythroid elements. Possibly at term, and in any case some days post partum, the plasma volume decreases, and it returns to normal within at most 2 weeks post partum. Studies of specific gravity, moisture content and protein concentration in plasma during pregnancy indi-

cate that the increase of the plasma volume, at least in part, is equivalent to simple hydremia.

The red cell mass probably varies less than the plasma volume, but on this point the evidence is uncertain.

The total iron requirements during pregnancy probably amounts to at least 600 mg. This amount probably far exceeds the menstrual loss of iron during a similar period. It is conceivable, therefore, that a slight iron deficiency may arise during pregnancy, at least if absorption of iron from the food remains unchanged.

*

Iron Metabolism in Pregnancy.

In the foregoing it was proved that in pregnancy the requirements of iron are probably quite considerable. Therefore it is interesting briefly to discuss the metabolism of iron during pregnancy.

The absorption of iron salts depends on several, in part unknown, factors. The functional state of the gastro-intestinal tract (HAHN *et al.* 1942) and the type of salt (MOORE *et al.*) seem to be of importance. The iron tolerance test in normals may suggest that the absorption of iron is good even if there is no reason to suppose that the iron depots in the organism are depleted. As regards iron supplied with the food, other nutritional factors are also of importance (BLIX 1947).

The hydrochloric acid in the stomach converts the iron in the food into an ionizable and absorbable form. The acid environment prevents the subsequent formation of insoluble compounds between iron and phosphates, amino acids and proteins (MOORE 1940). However, VAHLQUIST (1941), among others, has shown that in histamine refractory achylia reduced iron may considerably increase the serum iron level.

Naturally it is conceivable that in achylia the availability of food iron is reduced. The frequency of achylia in pregnancy has consequently been studied by several investigators. STRAUSS and CASTLE (1932) found a high frequency of hypochylia and achylia during pregnancy and connected these findings (as well as dietic factors) with the development of anemia in pregnancy. DAVIES and SHELLEY (1934), STEVENSON (1938) and FOWLER and BARER (1940) support this view, whereas a correlation between anemia of pregnancy and acidity is denied by, among others, BETHELL (1936), WATSON (1938), LABATE (1939) and HARJOLA (1946). LUNDHOLM (1939) has shown that achlorhydria in hypochromic anemia (colour index < 0.75) in only about 50 per cent of the cases is an integral feature of the disease and therefore cannot the essential reason for hypochromic anemia.

The absorption of iron salts is probably greater in pregnancy, at least in the latter stages. HAHN, WHIPPLE *et al.* (1942) in 14 pregnant

women during the latter part of pregnancy thus found an absorption of radioactive iron 2—10 times greater than in non-pregnant women. "The Vanderbilt Cooperative Study of Maternal and Infant Nutrition," according to DARBY and others (1947), is said to bear this out. The increased absorption of iron at the end of pregnancy is also indirectly confirmed by experiments with perorally administered iron. Thus, GUGGISBERG (1941) in an iron tolerance test on pregnant women found an increase of the serum iron value to 400 γ per cent. RENAER (1942) tested the iron tolerance of 13 women by giving each of them 225 mg ferrous chloride in 400 cc. H_2O before and after delivery. Before delivery the mean increase was 229 γ per cent and after it 102 γ per cent. LAURELL (1947) has shown that the iron-binding capacity of serum increases in the 6th month of pregnancy and attains its maximum in the 9th when it lies about 200 γ per cent above normal. This probably explains Renaer's findings.

Iron balance tests during pregnancy suffer from the same weaknesses as such tests carried out at other times: methodological difficulties and too short periods of observations on too small materials.

COONS (1932) in 9 pregnant women found a positive balance in 22 of 23 experiments at different stages of pregnancy. The average intake of iron was 14.7 mg daily. The balance varied between +0.88 and +6.97 mg per day and it was negative in one case only. "In general, retentions during the first 6 months of pregnancy were in excess of the calculated probable fetal demands, whereas during the last of the period they did not equal it,"...

TOVERUD (1935) made 20 iron balance tests on 15 pregnant women in the last 4 months of pregnancy. When the daily iron intake was less than 13 mg there was a negative balance and this also occurred occasionally when the intake was 15 mg.

During the last 63 days of pregnancy and the first 12 days post partum BETHELL (1936) found in one case a balance of ± 0 with a daily intake of 7.1 mg of iron together with vitamins A, B, C and D and an intake of 80 gm proteins. Both mother and fetus had high blood values. Therefore he assumed that the essential iron requirements of the pregnant woman are very small.

In a material of 14 cases put on a diet containing varying amounts of food iron, DIECKMANN *et al.* (1943) found that during pregnancy the iron balance on the whole is positive even if fetal requirements are taken into account.

On the basis of these balance tests, 15 mg of iron daily with the food has been considered the minimum requirements during pregnancy (COONS 1932, MACY and HUNSCHER 1934). TOVERUD (1935) and FOWLER and BARER (1940), however, have put the requirements at 20 mg. Judging by the above and also by the fact that food iron is available in varied quantities (WIDDOWSON and McCANCE 1936), it appears that at present

it is probably impossible to define with certainty any such "lower limit."

As regards the excretion of iron during pregnancy, there are no valid grounds for assuming anything abnormal; the elimination with urine and faeces is probably negligible.

Lastly, a few words will be said with respect to the size of the iron depots during pregnancy. It has often been assumed that at this time the iron depots become depleted. In man there are no direct proofs of this but MACKAY'S (1935) studies, for example, which suggest that children of anemic mothers often become anemic during the first year of life, indicate that the reason may be a reduction in the size of the maternal iron depots. Animal experiments with female rats (ALT 1938) show that during pregnancy a low iron diet causes the iron depots in both mother and fetus to be markedly reduced with anemia as a consequence. WIDDOWSON and McCANCE (1948) by animal experiments succeeded in proving that pregnancy reduces the iron content in the liver and that reaccumulation is slow.

*

Anemia in Pregnancy.

The following will deal solely with anemias associated with pregnancy.

Classification. Previously, the classification was based on the supposed reason for the anemia. Nowadays a morphologic classification is most usual and one of its main advantages is simplicity. WINTROBE'S scheme is usually adhered to (p. 288 in *Clinical Hematology*).

Etiology. Normocytic "anemia" or slight increase of the mean corpuscular volume (DIECKMANN *et al.*) as a rule has been thought to depend on hydremia and, according to WINTROBE (1934), simple microcytic anemia has the same cause. The lowering of the blood values, which probably is chiefly due to hydremia, has therefore been termed e. g. physiologic anemia of pregnancy (GRAM) and pseudoanemia (SCHULTZ). The best would probably be not to use the term anemia in connection with this condition.

The hypochromic, microcytic type of anemia, which according to most authors is the commonest form of anemia of pregnancy (excepting LABATE 1939), has been thought to depend on iron deficiency.

A macrocytic type of anemia has often been observed in poor districts by BETHELL *et al.* However, Bethell assumes that the macrocytosis is better interpreted as spherocytosis. The alleged reason is protein deficiency. The macrocytic anemia just mentioned is probably not of the same type as the so called pernicious anemia of pregnancy. Since this latter form of anemia is very rare except in certain geographic regions in Asia, especially India, I shall not deal with it here and the reader is referred to CALLANDER'S excellent treatise of 1944.

Table 3. *Incidence of anemia in pregnancy, according to different authors.*

Asterisked mtrls. identical. (Abbreviations see table 1.)

Authors	Year	Hemoglobin method	Lowest limit for normality, Hb. in per cent or gm/100 cc blood, R.B.C. in millions	n	Anemia frequency in per cent
Galloway	1929	Sahli	65 Hb., 4.00 R.B.C.	382	65
Jerlov	1929	A-rieth	70 Hb.	1143	26
Lyon	1929	Sahli	70 Hb.	177 (3rd T.)	32
Bland et al.	1930	Dare	3.5 R.B.C.	1000	47 (57 in 3rd T.)
Moore, J. H.	1930	Dare		300	50
Schrumpf	1930	Ha	13.0	554	>60
Esch	1932	Sahli	(70 Hb.) ev. 60 %	700	(55) ev. 8.7 %
Strauss and Castle	1932	Sahli		20	ca 50 (11 of 20)
Schultz	1933	Sahli	60 Hb., 3.0 R.B.C.	349	3
Davies and Shelley	1934	—		51	12
Davis and Walker	1934	H.-H.	70 Hb., 3.5 R.B.C.	158	43
Jerlov	1934	A-rieth		145	23—29
Richter et al.	1934	Sahli		61	most
Davidson, Fullerton and Campbell	1935*	Ha	11.7	819	70
McGeorge	1935	Hel.	10.0	100	16
Toverud	1935	Sahli	75 Hb., > 4.3 R.B.C. or 46 mg % iron	200	31
Adair, Dieckmann and Grant	1936	Newc.	10.16 Hb., 3.36 R.B.C. and 33.11 H-t	7835	12
Bethell	1936	Sahli	11.3 Hb., 3.7 R.B.C.	66	70 (27 macroc.)
Boycott	1936	Ha	11.0 Hb.	222	22
Corrigan and Strauss	1936	Sahli	10.9 one week p.p.	100	24 one week p.p.
Jacobi	1937	Sahli	75 Hb., 3.7 R.B.C.	318	43
Reid and Mackintosh	1937	Ha	9.7 Hb.	1108	10
Davidson and Fullerton	1938*	Ha	11.0 Hb.	819	50
Watson	1938	Sahli	7.70 Hb.	550	5
Bethell et al.	1939	Sahli	10.0 Hb., MCH 26 $\gamma\gamma$ (3.5 R.B.C., MCV > 97 c. μ)	158	54 (27 macroc.)
Eskridge	1939	Sahli	11.9 Hb. in 3rd T.	1000	38
Labate	1939	Sahli	11.6 Hb., 4.0 R.B.C.	307	72 at term
Bethell and Blecha	1942	Sahli		234	33 (7 macroc.)
Bethell et al.	1943	Sahli		484	25
Evans	1943	Sahli-Adams	8.7 Hb. ?	117	33
Elliott	1944	Ha	11.0 Hb.	48	58
Harjola	1946	Sahli	70 Hb.	220	55

Incidence. The frequency of anemia depends on the lower limit for normal values. In pregnant materials this lower limit is often drawn arbitrarily with the result that the frequency of anemia changes from investigation to investigation. See table 3.

The lower limit set by DIECKMANN and WEGNER (1934), viz. 10 gm hemoglobin per 100 cc. of blood, was calculated on the basis of the blood volume estimations of the authors. As the method of carrying out such estimations suffers from considerable errors, the limit 10 gm hemoglobin per 100 cc. blood should not be given undue importance. ELLIOTT (1944) stated that the lowest normal hemoglobin value during pregnancy is 9 gm per 100 cc. blood; provided, however, that the colour index is close to 1.0, and that the mean corpuscular diameter as well as its standard deviation and coefficient of variation and the mean corpuscular volume lie within normal limits. In my view such distinctions seem justified. On the basis of my own normal material, this question is discussed at length in chapter 3.

If, as often has been the case, a lower colour index is found together with a low hemoglobin value (e. g. STRAUSS and CASTLE 1932, RICHTER *et al.* 1934, BOYCOTT 1936, BETHELL *et al.* 1936, HARJOLA 1946), the changes in the *entire* material must always be studied. Thus, a normal material selected at random may show a significant correlation between hemoglobin and colour index. (In my material of 98 healthy, non-pregnant women the coefficient of correlation between hemoglobin and mean corpuscular hemoglobin is 0.59 ± 0.066 .) Cases with a lowered colour index may consequently be the result of normal variation. Whatever the circumstances, the term anemia is unjustified unless it is conclusively proved that the low colour indices are not results of normal variation.

Prognosis and Treatment. Supposing, as pointed out above, that we disregard pernicious anemia of pregnancy and certain other extremely rare forms of anemia, the prognosis will be good.

Lowered blood values with normal size blood corpuscles and normochromia is alleged not to require treatment and, besides, not to be susceptible to treatment. GUGGISBERG (1941) considers, however, that iron salts should be administered also in such cases.

On the other hand, practically all authors are agreed that a hypochromic, microcytic change of the red cells during pregnancy requires treatment with iron salts in the usual manner and with the usual results.

DIECKMANN *et al.* (1948 and earlier) disagree with this. However, judging by tables in the paper by TALSO and DIECKMANN (1948), there seems to be a stronger tendency to improvement in cases of microcytosis treated with iron than in controls not so treated. (The course of treatment lasted 21 days and the dosage was 1 gm of ferrous sulphate daily.) PLASS (1936) assumed that a certain part of the improvement attributed to iron medication in pregnancy may depend on physiologic concentration of the blood at the end of pregnancy, and ADAIR *et al.* (1936) emphasized the spontaneous hemoglobin increase at term which has been alleged by DIECKMANN and WEGNER (1934).

On the whole, the Review of Literature makes the problem clear. My main aims were:

To describe the changes in some blood characteristics during and after pregnancy and to learn the factors causing this, by following a comparatively large material, selected at random, of healthy, pregnant women. The blood characteristics in question are: hemoglobin, red blood cells, hematocrit, corpuscular values and serum iron.

To establish the effect of iron therapy in pregnancy.

CHAPTER 2.

Methods.

On each occasion we determined the amount of the hemoglobin, the red cell and hematocrit count, and the serum iron value. The samples were taken in the mornings, usually between 8—10, after 15—30 minutes rest. Double determinations were made throughout.

Cubital venous blood was used for the serum iron determinations. The other determinations were made with capillary blood from a fingertip that had been massaged for 3—5 minutes and, to ensure a plentiful flow of blood, the puncturing needle was inserted deeply into the fingertip. As far as possible the cubital blood, too, was taken without stasis.

The **hemoglobin** quantity in the blood was determined with the aid of Autenrieth-Königsberger's hemometer. Through the courtesy of Prof. H. Enghoff of the Department of Physiology, Uppsala University, the apparatus was standardized, with reference to the oxygen capacity of the blood, on three occasions: 27/3, 1946; 21/11, 1947; 18/2, 1948. The results of the three standardizations were practically identical. The equation for the last standardization is $Hb \% = 11.8 - 1.221 S$, where S denotes the scale readings on the hemometer. $100 \% = 15.3$ gm. Hb per 100 cc. blood. (To correct for pipetting errors, each hemoglobin value was multiplied with the factor 0.992.) The same pipettes were used throughout.

The error of measurement, calculated on the basis of 1,886 double determinations, is not quite 1.5 per cent. When hemoglobin is determined as acid hematin the error has been put at about ± 10 per cent (BARKAN & OLESK 1937, HEILMEYER & VON MUTIUS 1938). However, in a paper, not yet published, ENGHOFF reports that in 15 standardizations of more than 70 blood samples the correlation between the hemoglobin quantity found by the acid hematin method (Autenrieth-Königsberger), and that obtained by determination of the oxygen capacity, constantly exceeded 0.99, often by a wide margin. At most, the de-

viation from the straight line (corresponding to the standard deviation) reached 1.5 per cent. Thus, the agreement is very good between active hemoglobin and hemoglobin assayed as acid hematin.

The number of **red corpuscles** per cubic millimetre of blood was determined by counting in a Zeiss' chamber, system Bürker, standardized by comparison with H. Enghoff's counting chamber which is precision-made both as regards subdivision and depth. One section only was standardized and used. The standardization was carried out by the assistant who later counted all the blood corpuscles in the material. In connection with the standardization, altogether 8,450 D-squares were counted, 169 being counted at each separate counting with an error of measurement of 2 per cent. Each D-square = $1/4,000$ c. millimetres. The correction factor for the section of the counting chamber used was +4.27 per cent. (Calibration of the pipettes showed that the dilution was $1/199.9$ instead of $1/200$, and this error was disregarded.) The error of measurement for 1,656 double determinations made is about 2.8 per cent. Each counting involved 100 D-squares.

Before counting, the suspensions of blood corpuscles were kept in Ellerman tubes which, as soon as possible after taking the specimens, were put into a blood mixer of H. Enghoff's design. The Ellerman tubes were carried in a holder on a disk mounted at right angles to the axis of rotation. The holders were displaced, by bending the disk so that the longitudinal axes of the Ellerman tubes and the axis of rotation subtended an angle of about 15 degrees. On the disk the holders were arranged in two concentric circles with 12 and 8 holders respectively, the distance from the outer circle to the centre of the axis of rotation being 5.5 cm and from the inner 3.5 cm. The speed of rotation was about 23 revs. per minute. Usually the tubes were spun around in the apparatus for an hour and never for less than 20 minutes.

The **hematocrit** determinations were carried out according to the principles laid down by Enghoff in 1937.

The radius of the centrifuge was 107 mm. and its speed 9,600—9,700 revolutions per minute. Enghoff has proved that at this speed the hematocrit value becomes constant after 4 minutes. Owing to the high pressure of 53.3 atmospheres, to which this process subjects the blood corpuscles, it may be assumed that the corpuscle are compressed a slight but constant amount. In addition to Enghoff's original report the technique is also described in a paper by NAESLUND 1949.

After drawing, the capillary blood it was stirred with a small granule of "Liquoid Roche" (anticoagulant) which, according to ENGHOFF (1937) and MOSSBERG (1939), does not affect the hematocrit value. The blood was then drawn up into a tube with an inner diameter of 0.4 mm. The graduated part of the tube comprises 100 divisions and is 70 mm. long. During the centrifuging process the graduated, precision-ground part

of the tube faces outwards; the tube is held in a metal holder which presses it against a rubber bung so that leakage is precluded. A magnifier designed by Enghoff makes reading very simple. In this manner it becomes possible to compute the corpuscular volume in per cent, without the necessity for drawing up blood to a given graduation, by reading the corpuscular volume and the total blood volume. The error of measurement, calculated on the basis of 1,886 double determinations, is rather more than 1 per cent.

The **serum iron** was determined according to the method developed in 1937 by HEILMEYER and PLÖTNER, as modified by B. VAHLQUIST (1941). The total quantity in the sample was accordingly computed by measuring the volumes of the various added reagents, and the trichloroacetic acid was distilled in vacuum to make it free from iron. The 7 cm. filter papers used were mostly of Munktell's manufacture, and they were treated with hydrochloric acid to take out any traces of iron. The pipettes used and the microburettes (for titration with ammonia and sulphuric acid) were carefully weighed and so exact that the values did not have to be corrected. The same pipettes were used throughout. The blank was consistently about or just above 20 γ per 100 cc.

In the majority of titrations (66 to be exact) I could check the serum iron determination by means of a known iron solution. The agreement was good between calculated and found values.

The error of measurement for the 1,466 double determinations was about 4 per cent.

The **statistical methods** adopted by the author are generally recognized procedures which are described, for example, in Dahlberg's and Tippet's textbooks. The probability (P) was found in tables in Bonnier-Tedin's textbook.

Only some details require comment.

The sum of squares "within classes" can naturally be subdivided anew in the same manner as the total sum of squares. Whenever such subdivision was required, I performed the statistical operations as though the subdivision were hierarchical, but the estimation of significance did not take place as in the hierarchical subdivision. (See for instance table 11, p. 33).

For the purposes of this paper, the selected level of significance has a probability (P) lying on 0.01. If $0.01 > P > 0.001$, the significance is as a rule termed statistically probable. A probability level of 0.001 or less is considered statistically significant, and this is also the case if P is greater than but close to 0.001.

CHAPTER 3.

Material.

The main material comprises 136 healthy, pregnant women between 18 and 43 years old (only 5 of these were unmarried when the child was born). Originally the number was larger but all those women were excluded who stopped coming to the periodic examinations, contracted serious complications or gave birth to premature children weighing less than 2,200 gm. (3 cases). The complications concerned were gestosis, 9 cases; grave vitium cordis; myomas operated on during pregnancy; and active pulmonary tuberculosis.

Here an important point deserves brief mention, viz. the problem of distinguishing between healthy and diseased subjects. As a rule this is not a difficult matter and is of no special consequence except as regards diseases of the blood. However, it so happened that none of the test persons had to be excluded for such disease at the first examination (one case was uncertain but is included all the same) when I followed the procedure laid down in Chapter 4. It should be noted, however, that anemia may be a troublesome source of error. If persons with anemia are sorted out on the basis of the blood values, the method of sorting at the same time fixes the lower limit for the variability. If such persons are not sorted out the material will be misleading. It must therefore be considered unusually fortunate that I did not have to face these problems, and, obviously, in a larger material these difficulties would be unavoidable.

The test persons were selected at random in so far as all healthy, pregnant women who applied for examination at the Clinic for Women's Diseases, Uppsala, during the first half of their pregnancy, in the first half of 1947, were included in the test material. The test persons were then reexamined every second month or so and, in a varying number of cases (see further on) during and after delivery. If, on a given day, an excessive number of women applied, only as many were included in the material (in the order of arrival) as was thought suitable.

For the purposes of this study, pregnancy was divided into 5 periods of 8 weeks. The distribution of the examinations on periods and weeks of pregnancy appears in table 4.

At times the same test person was examined twice during the same period. If the examinations took place on two consecutive days, which was the rule, means were then computed. In other cases one value only was included for each period, which was so chosen that each quarter-period showed approximately the same number of examinations.

Statistically, an investigation of the variation of the blood values

Table 4. *Number of subjects in the various weeks of pregnancy in the main material.*

Lunar month of pregnancy	Weeks of pregnancy	No.	Lunar month of pregnancy	Weeks of pregnancy	No.
I—II (Pd ₁)	6—7	18	VII—VIII (Pd ₄)	24—25	35
III—IV (Pd ₂)	8—9	26		26—27	26
	10—11	27		28—29	25
	12—13	23		30—31	36
	14—15	25		<i>Subtotal</i>	122
	<i>Subtotal</i>	101	IX—X (Pd ₅)	32—33	24
V—VI (Pd ₃)	16—17	39		34—35	47
	18—19	23		36—37	43
	20—21	32		38—40	12
	22—23	28		<i>Subtotal</i>	126
	<i>Subtotal</i>	122		<i>Total</i>	489

during pregnancy may be conducted in two ways. Either the same persons may be studied throughout their pregnancy or different persons may be examined in each of the several periods of that condition. In practice a compromise between these two methods is probably the best from the point of view of the examiner. However, the first method is the more reliable, since anemic changes in the blood values at the end of pregnancy do not preclude "normal" values at its beginning. Obviously it is very difficult to keep the material uniform if new persons have been examined at different stages of the pregnancy. Tables 5 and 6 give a survey of how the material is composed in this respect.

It appears from tables 5 and 6 that in principle I have endeavoured to study the same cases ante partum and post partum. Of the 3 subjects who were examined only once, according to the tables, 2 had been given iron salts that had been administered by a physician other than myself, so that their blood values could not be included in the statistical analysis. In 130 instances the first examination took place before the end of the 19th week of pregnancy, in 3 during the 21st in 3 in the 23rd week. 101 cases were examined about 6 weeks after parturition. During the first 10 days after parturition, 10 patients were not examined, 60 were examined once or twice, 62 persons 3 times, and 4 more than 3 times.

The main material is subdivided into "urban" and "rural" domicile, despite the fact that the latter group contains only 28 subjects. Other grounds for subdivision were economic standard (arbitrarily fixed above and below 6,000 kronor annual income) and the number of previous births. The subdivisions were made to bring out some indication of the influence on the blood picture of dietic habits, living standard and num-

Table 5. *Total number of determinations per subject in the main material during pregnancy, one determination only per period of 8 weeks.*

Number of deter- minations	Number of cases	Total
1	3	3
2	4	8
3	43	129
4	81	324
5	5	25
Total	136	489

Table 6. *Total number of determinations per subject in the main material.*

Number of deter- minations	Number of cases	Total
1	2	2
2	1	2
3	9	27
4	4	16
5	7	35
6	27	162
7	39	273
8	30	240
9	15	135
10	1	10
11	—	—
12	1	12
Total	136	914

ber of previous births. Of the test persons included in this material, 55 belonged to the higher income group and 81 belonged to the lower. Consequently, it would have been preferable to draw the income line rather lower, but this was impossible to foresee when the study was commenced.

In the age group 18—43 years, the age as such is unlikely to influence the blood values in healthy women (Wintrobe, Enghoff and my normal material). The constancy of the normal values does not prevent older pregnant women from exhibiting greater changes than young ones. The material has therefore been subjected to detailed statistical treatment. It can be seen from table 7 that the number of older women, even if the limit is put as low as thirty years, is fairly small and the likelihood of solving the problem of the influence of age on this material is therefore, unfortunately, quite remote. Table 7 shows the distribution of the material with respect to age and the number of previous confinements.

Table 7. *Age distribution in the main material with regard to the number of earlier deliveries. Also age distribution in the normal material.*

Age, years	No. of earlier deliveries			Total	Normal material
	0	I	> I		
18—19	3	—	—	3	2
20—21	10	9	—	19	14
22—23	12	6	1	19	19
24—25	10	5	2	17	14
26—27	8	7	4	19	21
28—29	5	8	4	17	15
30—31	5	3	5	13	7
32—33	2	6	2	10	—
34—35	2	3	3	8	1
36—37	—	2	4	6	1
38—39	2	1	1	4	3
40—41	—	—	—	—	—
42—43	—	—	1	1	1
Total	59	50	27	136	98

The age median in the main material lies at 27.1 years, the lower quartile at 23.3, and the upper at 31.2 years. In the normal material the median lies at 26.0 years, the lower quartile at 22.9 and the upper at 28.5 years. We thus have to deal with skew distributions, especially in the normal material, but their mutual agreement is comparatively good.

Throughout, I did my best to obtain as reliable dietic case histories as possible. In this respect, naturally, the difficulties were great but it is unlikely that any of the cases had subsisted on a markedly deficient diet. As a general rule the diet seems to have been varied, with animal proteins, milk, vegetables and meat. Some which had drunk no milk and others who did not eat meat will be discussed briefly in Chapter 5.

The complications during pregnancy in the main material were the following:

20 persons vomited for more than 2 months during pregnancy, 7 had gastro-intestinal troubles of fairly grave nature; 36 had previously been treated with iron salts, 21 of these in connection with an earlier pregnancy. The suspected anemia had in no case been serious or subjected to clinical examination.

Persons given iron preparations during the current pregnancy were thereafter excluded from the statistical treatment.

In the main material the following complications attended labour and puerperium:

a. 24 cases of transient albuminuria during or after parturition, without increased blood pressure.

- b. 5 cases of afebrile infection of the urinary tract.
- c. 1 case of pyelitis, max. temp. $38^{\circ}.1$ some days, treated with sulfonamid preparations.
- d. 12 cases of saprophytic endometritis attended by a brief rise in temperature, in one case up to $38^{\circ}.3$ the other not above $38^{\circ}.1$. In 2 of these cases the sides of the uterus were painful to palpation.
- e. 1 case of lymphangitis mammae with a single rise in temperature and rapid regression.
- f. 1 case of pelvis justo minor, cesarotomized, uneventful recovery.
- g. 2 cases of forceps delivery without complications.

Since infectious complications were very transient, I have thought it justifiable to assume that their influence on the blood values were negligible and the subjects in question were therefore included in the statistical analysis. The mean duration of the hospitalization for these patients with complications was 10 days (in 1948 the mean lying-in period at the maternity clinic was 9.3 days). As in the case of the main material during pregnancy, all cases given iron treatment were excluded from the statistical analysis.

The intra-partum hemorrhage is dealt with in Chapter 6.

The investigation also includes 53 pregnant women who, during the middle and latter half of pregnancy, were given massive iron doses for comparatively long periods. These were selected during the last six months of 1948 according to the same principles as applied to the main material.

In Chapter 4 is described a normal material comprising 98 cases.

CHAPTER 4.

Normal Material and Concepts of Anemia.

The normal material consists of 98 nulliparous women, chosen at random, between 18 and 43 years old. Most of them were nurses, nursing trainees and other female employees at the University Hospital, Uppsala. This material was collected during the first 3 months of 1948, one case only being from May 1947. The age distribution appears in table 7 and the blood values in table 8.

The material includes 13 subjects 30 years old or more. A comparison between the age groups 18—30 and 30—43 shows no significant differences in blood characteristics.

It is very interesting to compare this material with already existing normal Uppsala materials. See table 9.

In Enghoff's material the hemoglobin was determined by the oxygen capacity method in 52 cases and colorimetrically (as acid hematin)

Table 8. *Mean and standard error of the mean, $M \pm \varepsilon(M)$, standard deviation, σ , coefficient of variation, v for red corpuscles and serum iron in 98 non-parous normal women in 18—43 years of age.*

Blood characteristics	$M \pm \varepsilon(M)$	σ	v	Real mean ¹ $\pm 2.633 \times$ standard deviation
Hemoglobin (gm/100 cc blood)	12.0 $\pm$ 0.07	0.72	6.0	10.0 — 14.1
Red cells (mill./c.mm)	4.20 $\pm$ 0.03	0.26	6.2	3.44 — 4.96
Hematocrit (vol. per cent)	39.0 $\pm$ 0.22	2.14	5.5	32.8 — 45.2
M.C.H.C. (per cent)	30.9 $\pm$ 0.15	1.46	4.7	26.7 — 35.1
M.C.H. ($\gamma\gamma$)	28.7 $\pm$ 0.17	1.72	6.0	23.7 — 33.7
M.C.V. (c. μ)	93.0 $\pm$ 0.5	5.3	5.7	77.7 — 108.3
Serum iron (γ /100 cc; 97 cases)	126.8 $\pm$ 3.1	30.8	24.3	37.5 — 216.1

¹ In this case the real mean denotes the mean $\pm t \times \varepsilon(M)$ which implies that with a probability of 0.99 it lies within these limits.

in 97. His material is, moreover, not exclusively from Uppsala but is composed of 3 materials from different latitudes: Skellefteå, Uppsala and Lund, the difference between the materials being negligible. The influence of age on the material was so small that it could be disregarded. In Vahlquist's and Nilson's materials the hemoglobin was determined colorimetrically as acid hematin.

Owing to the standardization of the apparatus, the hemoglobin values in tables 8 and 9 may well be compared. Whereas the hemoglobin values in table 9 are approximately equal, the mean value in my material is markedly discrepant as compared with the means of the other authors. A similar discrepancy is also found in the red cell count in the two comparable materials (Enghoff's and mine), but the hematocrit values agree. As regards serum iron, my values are higher than both Vahlquist's and Waldenström's. The former difference may be due to random variation, and the latter is not statistically significant.

Thus, in the normal materials of the cited investigators and myself the hemoglobin values are highly discrepant, and this applies also to the red cell count in the present material and Enghoff's. The possibility that my normal material includes many cases of anemia may probably be disregarded, since the coefficient of variation for red cells, hemoglobin and hematocrit, is low; the distribution curve for e. g. hemoglobin is roughly normal and the mean serum iron value is not lower than in comparable normal materials.

The colorimetric method of determining hemoglobin as acid hematin has been discussed in the chapter on methods. The personal factor, however, can be a serious source of error (ODIN and WERDINIUS 1934). NILSSON (1948) has a discrepancy in hemoglobin content of about 1.1

Table 9. *Earlier published normal materials from Uppsala for blood characteristics. Some of the values have been calculated by the present author.*

($M \pm \varepsilon(M)$ = mean $\pm$ standard error of the mean, σ = standard deviation, v = coefficient of variation.)

Blood characteristics		Author			
		H. Enghoff 1937 Venous and capillary blood	B. Vahlquist 1941 Capillary blood	J. Walden- ström 1946	F. Nilsson 1948 Venous blood
R.B.C. (mill./c.mm)	No.	149	49	—	64
	$M \pm \varepsilon(M)$	4.7 ± 0.03	4.4 ± 0.05	—	4.3 ± 0.05
	σ	0.33	0.32	—	0.42
	v	7.1	7.3	—	9.8
Hb. (gm/100 cc blood)	No.	149	50	—	64
	$M \pm \varepsilon(M)$	13.4 ± 0.10	13.5 ± 0.12	—	13.6 ± 0.13
	σ	1.26	0.87	—	1.03
	v	9.4	6.4	—	7.6
Hematocrit (vol. per cent)	No.	97	—	—	64
	$M \pm \varepsilon(M)$	39.0 ± 0.29	—	—	40.2 ± 0.25
	σ	2.90	—	—	2.00
	v	7.4	—	—	5.0
M.C.V. (c. μ)	No.	—	—	—	64
	$M \pm \varepsilon(M)$	(83)	—	—	92.3 ± 1.0
	σ	—	—	—	7.7
	v	—	—	—	8.3
M.C.H.C. (per cent)	No.	—	—	—	64
	$M \pm \varepsilon(M)$	(34.4)	—	—	34.0 ± 0.28
	σ	—	—	—	2.24
	v	—	—	—	6.6
M.C.H. ($\gamma\gamma$)	No.	—	49	—	64
	$M \pm \varepsilon(M)$	(28.5)	30.7 ± 0.3	—	31.5 ± 0.38
	σ	—	2.0	—	3.01
	v	—	6.5	—	9.6
Serum iron (γ /100 cc)	No.	—	50	15	—
	$M \pm \varepsilon(M)$	—	123.0 ± 4.5	113.2 ± 8.2	—
	σ	—	31.6	31.9	—
	v	—	25.7	28.2	—
Age in years		18—59	20—30	—	20—40

g./100 cc. blood between two otherwise very similar normal materials from Umeå and Uppsala. In his opinion the discrepancy is due to two different assistants having made the determinations, an apparently well founded assumption. The low hemoglobin values in my normal material may in part be attributed to bias on the part of my assistant. Thus the actual hemoglobin value might perhaps be higher. Since the

same assistant has made all the hemoglobin determinations in the total material (except for a number of cases given iron treatment during pregnancy, see Chapter 8) and the error is systematic, which is evident from the error of method for the entire material and the coefficient of variation in the normal material, the logical conclusion is that the hemoglobin values do not with certainty indicate the actual hemoglobin content but must be considered in relation to the normal material.

The red cell count discrepancy in Enghoff's and my material is more difficult to explain (see Chapter on Methods) but in this case also the error is systematic and therefore the same interpretation as for the hemoglobin values should apply.

Generally speaking, anemia denotes a reduction in the values for hemoglobin, red cells and hematocrit per unit volume of blood so that these values lie below a given level which is considered to be the lower limit for the normal variation or, rather, a certain percentage of it. This would not be a problem if the blood characteristics were distributed along a normal curve and this curve practically came to a stop at the point where anemia starts. This is not the case, however, for anemic values overlapped the distribution of the normal blood values. Naturally, the only conclusive proof of anemia is its effects. But, particularly when the anemia is mild, the symptoms are so indefinite and vague that it is difficult to decide whether or not they are present. Owing to these circumstances, the problem of where to draw the line between anemic and normal subjects must be considered a very difficult one.

The literature on hematology contains a large number of investigations with the object of laying down normal limits for blood values. With a high degree of probability the patient would therefore be anemic below a such lower normal limit. WINTROBE (1933 and 1934) has made a comprehensive summary of his own and earlier investigations, and later authors vary only slightly. (For tabulation of normal variation see WINTROBE 1933 and 1934 and Wintrobe's Clinical Hematology, BIERRING 1940 and NILSSON 1948. For serum iron variation see VAHLQUIST 1941, LAURELL 1947, and NILSSON 1948.)

My normal material differs from others in the literature in the same manner as from the Uppsala materials discussed previously, except for the hematocrit value. (The reason for the latter difference must be looked for in the method.) In table 8 I have therefore given the "normal range" for the different blood characteristics. With the procedure used here only about 1 per cent of the normal variation in women should fall outside the given limits.

Naturally, a blood value needs not be normal because it lies within the given limits. In doubtful cases the corpuscular values and possibly serum iron value are helpful. Furthermore, if the values just mentioned are normal and the hemoglobin content is less than 10.0 gm. per 100 cc. blood (cf. table 8), the reason may be dilution.

Other limits for normal blood characteristics than the ones given may naturally be selected, and in clinical work it is surely advisable to use stricter limits, but as the matter is of slight interest for the following discussion I have refrained from making another conceivable delimitation.

In this connection it should be noted that there is no possibility of directly comparing pregnant and non-pregnant women. In the review of earlier literature I have shown that a certain, quantitative, unknown dilution (hydremia) of the blood must be taken into account, and I wish to stress that one of the main objects of the present study is to define the *characteristic* changes in the blood values during pregnancy. The regularly present reduction in the blood values taking place during pregnancy and progressing without subjective symptoms may a priori be considered "physiologic" rather than anemic and should not be so termed unless suggested by other factors than by a drop in hemoglobin, red corpuscles or hematocrit below an arbitrary level. So, at least during the early stages of pregnancy, no alternative remains other than to consider the variation in the blood characteristics a normal complement to pregnancy in women who are healthy according to the above principle, unless there are marked changes especially in the corpuscular values.

CHAPTER 5.

Blood Characteristics in the Main Material during Pregnancy.

Influence of Number of Earlier Deliveries, of Social Conditions, and of Age.

The material is described in Chapter 3. Table 10 and Diagram 1 contain the mean blood characteristics and the standard deviations in each of the 5 periods of pregnancy.

It appears that all blood characteristics, except mean corpuscular hemoglobin concentration, decrease during pregnancy, and that for all the blood characteristics the respective standard deviation is nearly constant.

In the first place it is essential to find out to what extent these changes may be due to random variation or may be considered statistically significant. In order to solve this problem we shall first apply analysis of variance. This will only tell us if changes occur in any of the periods of pregnancy and not in which period the change is greatest, nor if there is a continuous tendency. These questions will be dealt with later.

Table 10. Mean blood values in the different periods during pregnancy in the main material. (Abbreviations see table 19).

Blood characteristics			Period during pregnancy—average				
			Pd ₁ 7 weeks range 0— 8 w.	Pd ₂ 11 weeks range 8— 16 w.	Pd ₃ 19 weeks range 16— 24 w.	Pd ₄ 28 weeks range 24— 32 w.	Pd ₅ 35 weeks range 32— 40 w.
No. of cases:			18	101	122	122	126
Hemoglobin (gm/100 cc blood)	$M \pm \epsilon (M)$		10.9 $\pm$ 0.16	10.8 $\pm$ 0.07	10.3 $\pm$ 0.07	9.9 $\pm$ 0.07	9.8 $\pm$ 0.08
	σ		0.66	0.73	0.79	0.83	0.91
	ν		6.1	6.7	7.7	8.3	9.3
Red cells (mill./c.mm)	$M \pm \epsilon (M)$		4.16 $\pm$ 0.10	4.05 $\pm$ 0.032	3.79 $\pm$ 0.028	3.69 $\pm$ 0.024	3.82 $\pm$ 0.030
	σ		0.41	0.33	0.31	0.27	0.33
	ν		9.9	8.1	8.1	7.3	8.7
Hematocrit (vol per cent)	$M \pm \epsilon (M)$		38.3 $\pm$ 0.59	37.2 $\pm$ 0.23	35.2 $\pm$ 0.26	33.7 $\pm$ 0.26	33.7 $\pm$ 0.28
	σ		2.5	2.3	2.9	2.9	3.1
	ν		6.6	6.2	8.2	8.5	9.2
M.C.H.C. (per cent)	$M \pm \epsilon (M)$		28.5 $\pm$ 0.31	29.2 $\pm$ 0.15	29.1 $\pm$ 0.14	29.5 $\pm$ 0.15	29.3 $\pm$ 0.12
	σ		1.3	1.5	1.5	1.6	1.4
	ν		4.6	5.1	5.3	5.5	4.8
M.C.H. ($\gamma\gamma$)	$M \pm \epsilon (M)$		26.4 $\pm$ 0.44	26.8 $\pm$ 0.18	27.1 $\pm$ 0.18	26.9 $\pm$ 0.18	25.9 $\pm$ 0.16
	σ		1.9	1.8	2.0	2.0	1.8
	ν		7.0	6.8	7.4	7.3	6.8
M.C.V. (c. μ)	$M \pm \epsilon (M)$		92.7 $\pm$ 1.9	92.2 $\pm$ 0.58	93.4 $\pm$ 0.64	91.5 $\pm$ 0.56	88.4 $\pm$ 0.51
	σ		8.2	5.9	7.1	6.2	5.8
	ν		8.8	6.4	7.6	6.8	6.5
No. of cases:			17	98	115	119	123
Serum iron	No. of earlier deliveries						
	0	$M \pm \epsilon (M)$	157.0 $\pm$ (10.7)	129.7 $\pm$ 4.2	139.8 $\pm$ 5.6	94.4 $\pm$ 3.8	86.9 $\pm$ 4.5
(γ/100 cc)	I	No.	8	46	51	54	55
		$M \pm \epsilon (M)$	150.0 $\pm$ (16.2)	129.7 $\pm$ 7.3	135.7 $\pm$ 6.5	94.4 $\pm$ 5.5	82.9 $\pm$ 4.6
>I		No.	5	35	41	43	46
		$M \pm \epsilon (M)$	105.7 $\pm$ (18.3)	105.2 $\pm$ 9.8	97.7 $\pm$ 7.3	94.5 $\pm$ 7.7	70.6 $\pm$ 4.8
0 — > I		No.	4	17	23	22	22
		$M \pm \epsilon (M)$	142.0 $\pm$ 9.1	125.5 $\pm$ 3.8	129.9 $\pm$ 4.0	94.4 $\pm$ 3.0	82.5 $\pm$ 2.8

Table 11 shows the result on this material of variance analysis with regard to periods of pregnancy (5 groups), number of earlier deliveries (3 groups), economic status (2 groups) as well as rural and urban domicile (cf. Chapter 3).

The differences between rural and urban domicile may be due to random variation, when the other sources of variation are eliminated. I have also investigated the relationship between rural or urban domi-

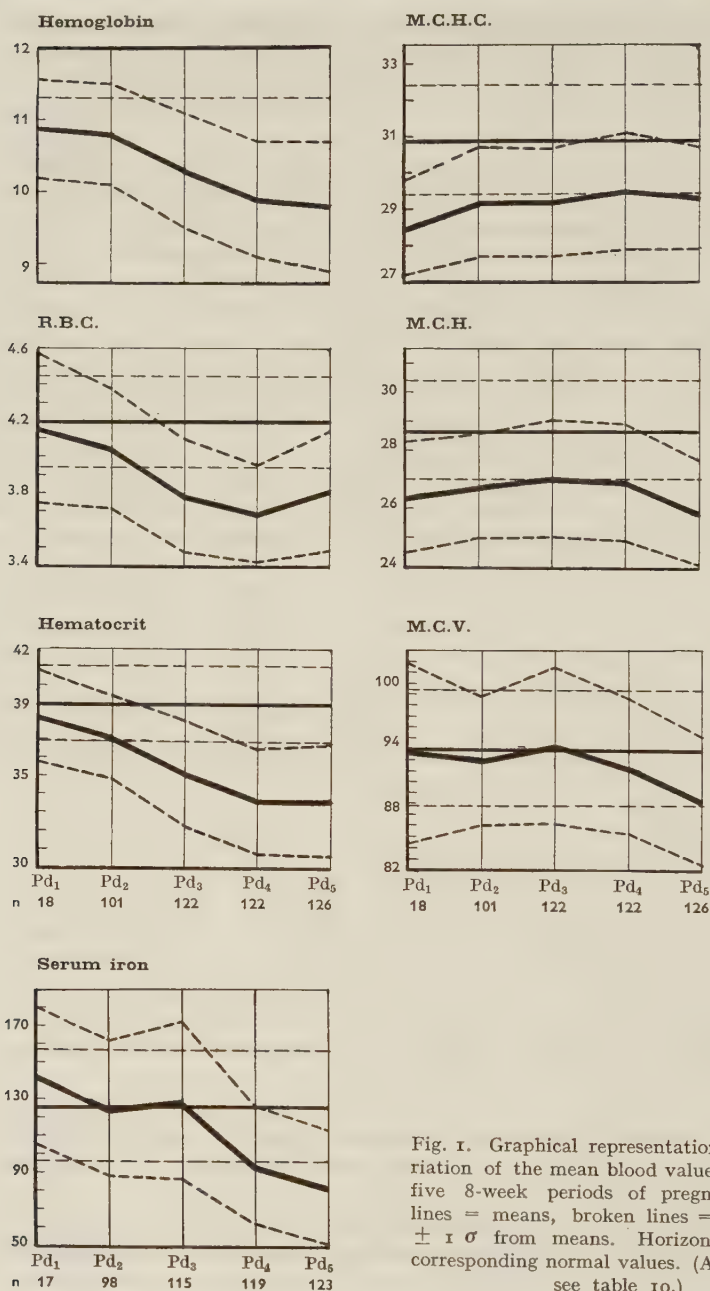


Fig. 1. Graphical representation of the variation of the mean blood values during the five 8-week periods of pregnancy. Solid lines = means, broken lines = distance of $\pm 1 \sigma$ from means. Horizontal lines = corresponding normal values. (Abbreviations see table 10.)

Table 11. *Analysis of variance of the main material during pregnancy with regard to the different divisions of the material.*

Blood characteristics (Class interval)	Source of variation	Degrees of freedom	Mean square	P
<i>Total for Hb, R.B.C. etc.:</i>		488		
Hemoglobin (0.2 gm/100 cc blood)	Between periods	4	471.3	(<0.001)
	Within »	484	16.7	
	Between no. of earlier deliveries	10	11.3	(>0.2)
	Within » » » »	474	16.8	
	Between income classes	14	26.3	(0.2—0.05)
	Within » »	460	16.5	
	Between country-town....	28	12.7	≈ 0.2
	Within » »	432	16.7	
Red cells (0.06 mill. per cc.m)	Between periods	4	667.1	(<0.001)
	Within »	484	27.6	
	Between no. of earlier deliveries	10	27.7	(>0.2)
	Within » » » »	474	27.6	
	Between income classes	14	24.4	(>0.2)
	Within » »	460	27.7	
	Between country-town....	28	33.1	≈ 0.2
	Within » »	432	27.4	
Hematocrit (0.5 vol. per cent)	Between periods	4	1091.7	(<0.001)
	Within »	484	32.0	
	Between no. of earlier deliveries	10	31.1	(>0.2)
	Within » » » »	474	32.0	
	Between income classes	14	26.0	(>0.2)
	Within » »	460	32.2	
	Between country-town....	28	29.7	>0.2
	Within » »	432	32.3	
M.C.H.C. (0.25 per cent)	Between periods	4	67.7	(0.2—0.05)
	Within »	484	36.1	
	Between no. of earlier deliveries	10	34.7	(0.2)
	Within » » » »	474	36.1	
	Between income classes	14	52.7	(0.2—0.05)
	Within » »	460	35.6	
	Between country-town....	28	39.1	>0.2
	Within » »	432	35.4	
M.C.H. (0.25 γγ)	Between periods	4	485.7	(<0.001)
	Within »	484	57.3	
	Between no. of earlier deliveries	10	96.0	(0.2—0.05)
	Within » » » »	474	56.4	
	Between income classes	14	99.7	(0.05—0.01)
	Within » »	460	55.1	
	Between country-town....	28	63.9	≈ 0.2
	Within » »	432	54.6	

(Table 11 continued.)

Blood characteristics (Class interval)	Source of variation	Degrees of freedom	Mean square	P
M.C.V. (1.0 c.μ)	Between periods	4	409.4	(<0.001)
	Within »	484	40.4	
	Between no. of earlier deliveries	10	94.6	(≈ 0.01)
	Within » » »	474	39.3	
	Between income classes	14	46.0	(0.2)
	Within » »	460	39.1	
	Between country-town....	28	49.0	0.2—0.05
	Within » »	432	38.4	
Total:		472		
Serum iron (5.0 γ/100 cc)	Between periods	4	2077.5	—
	Within »	468	51.8	
	Between no. of earlier deliveries	10	201.1	(<0.001)
	Within » » »	458	48.5	
	Between income classes	14	96.3	(0.05—0.01)
	Within » »	444	47.0	
	Between country-town....	28	49.2	>0.2
	Within » »	416	46.9	

cile, irrespective of income, within number of earlier deliveries. Here also $P \geq 0.2$; except for mean corpuscular volume, $0.2 > P > 0.05$, and mean corpuscular hemoglobin, $0.05 > P > 0.01$. It seems therefore permissible to disregard the classification by rural or urban domicile in the subsequent statistical treatment.

We now turn to the effect of economic status within number of deliveries. Here P is > 0.05 ; only for serum iron and mean corpuscular hemoglobin $0.05 > P > 0.01$. I have therefore neglected also the classification by income in the subsequent statistical treatment.

The effect of the number of earlier deliveries (within periods) on the blood characteristics is statistically random except for mean corpuscular volume and serum iron. For mean corpuscular volume $P \approx 0.01$, but by comparing the mean values between number of deliveries in each period it was found that the differences were negligible in two of the 5 periods. In period 0—8 weeks, moreover, (very few cases) the tendency is the opposite to that in periods 16—24 weeks and 24—32 weeks. In the latter 2 periods the mean corpuscular volume is lowest in multiparae. However, since the significance is only on the verge of "probable", I find no reason to give undue importance to the difference. Only a larger material can decide the question. Therefore, except for serum iron, I have disregarded the classification by number of earlier deliveries in the subsequent statistical treatment.

Within periods the number of earlier deliveries significantly affects

the serum iron value ($P < 0.001$). This is shown in table 10 which also shows that the dividing line runs between "one earlier child" and "more than one earlier child". It also appears that the differences are greatest in the first 3 periods and that they are negligible or non-existent in the last 2.

The effect of age is shown in table 12. Age probably cannot have any effect before the latter stages of the fertile period. These are very sparsely represented in the material, however, so the line was drawn at 34 years. The number of persons 34 years or older was 19.

The variance analysis with respect to the influence of age applies within periods of pregnancy. An additional classification was made,

Table 12. *Analysis of variance of the main material during pregnancy with regard to 2 age-classes, and concerning serum iron, also number of earlier deliveries.*

Blood characteristics (Class interval)	Source of variation	Degrees of freedom	Mean square	P
Hemoglobin (0.20 gm/100 cc blood)	Between periods.....	484		
	Between ages.....	5	14.5	> 0.2
	Within ages.....	479	16.7	
Red cells (0.06 mill./c.mm)	Between periods.....	484		
	Between ages.....	5	19.4	> 0.2
	Within ages.....	479	27.7	
Hematocrit (0.5 vol. per cent)	Between periods.....	484		
	Between ages.....	5	31.6	> 0.2
	Within ages.....	479	29.9	
M.C.H.C. (0.25 per cent)	Between periods.....	484		
	Between ages.....	5	43.4	> 0.2
	Within ages.....	479	36.0	
M.C.H. (0.25 $\gamma\gamma$)	Between periods.....	484		
	Between ages.....	5	125.1	0.05
	Within ages.....	479	56.6	
M.C.V. (1.0 c. μ)	Between periods.....	484		
	Between ages.....	5	20.8	> 0.2
	Within ages.....	479	40.6	
Serum iron (5.0 γ /100 cc)	Within no. of earlier deliveries	458		
	Between ages.....	15	30.1	0.2—0.05
	Within ages.....	443	49.1	
	Within periods.....	468		
	Between ages.....	5	96.1	(0.2—0.05)
	Within ages.....	463	51.3	
	Between no. of earlier deliveries.....	20	99.1	≈ 0.01
	Within no. of earlier deliveries.....	443	49.1	

eliminating the variation from number of earlier deliveries. As regards serum iron the influence of age was eliminated when the effect of the number of earlier deliveries was estimated.

No significant evidence of the influence of age can be traced. It is interesting to note, however, that the classification by number of earlier deliveries, according to table 10, yields a serum iron difference which now is only probable, but the tendency towards lower serum iron values in multiparae is the same above and below 34 years. The number of cases is very small, however, and the statistical analysis only reveals that the differences in blood values between the respective age groups cannot be very large. A far larger material is required to definitely decide the question.

Coming finally to the differences between the various periods of pregnancy, we find them significant for all blood characteristics except mean corpuscular hemoglobin concentration (P considerably lower than 0.001). The "period" differences for serum iron within number of earlier deliveries was found to have a $P < 0.001$.

SUMMARY. — Variance analysis applied to the material's blood characteristics during pregnancy has not revealed any remarkable differences as regards rural or urban domicile, income classes or age groups. These classifications are therefore disregarded in the subsequent statistical treatment. However, they will be discussed later in this chapter.

It seems possible that during pregnancy the serum iron value is higher in women who are pregnant for the first or second time than in others. The influence of age might be of some importance in this respect, but the material is far too small to clear up this question. The classification by number of earlier deliveries during pregnancy was retained for serum iron but not for other blood characteristics, since their differences may be accidental. (Mean corpuscular volume, however, shows a probable difference, but the tendency is variable.)

The blood characteristics decrease significantly during pregnancy. The changes of mean corpuscular hemoglobin concentration may be due to random variation, but during pregnancy its level is still significantly lower than in the normal material.

Main Material Compared with Normal Material.

I have chosen to compare the combined 1st and 2nd periods (0—16 weeks) and the fifth period (32—40 weeks) with the normal material; the result of the comparison is shown in table 13.

It appears from the table that as early as in period 0—16 weeks the hemoglobin, red cell, and hematocrit values are significantly lower than in the normal material. This also applies to mean corpuscular hemoglobin concentration and mean corpuscular hemoglobin, whereas the

Table 13. *Differences and standard error of the differences between the normal material and various periods in the main material (Abbreviations see table 10).*

Blood characteristics	Differences between			
	No.	Normal material and Pd ₁ + Pd ₂	No.	Normal material and Pd ₅
Hemoglobin (gm/100 cc blood)	217	1.21 ± 0.10	224	2.21 ± 0.11
Red cells (mill./c. mm).....	217	0.134 ± 0.041	224	0.384 ± 0.040
Hematocrit (vol. per cent) ..	217	1.67 ± 0.31	224	5.31 ± 0.35
M.C.H.C. (per cent)	217	1.85 ± 0.20	224	1.66 ± 0.19
M.C.H. (γγ).....	217	1.96 ± 0.24	224	2.86 ± 0.23
M.C.V. (c.μ)	217	0.90 ± 0.78	224	4.57 ± 0.74
Serum iron (γ/100 cc).....	213	-1.3 ± 5.0	221	44.3 ± 4.4

differences for mean corpuscular volume and serum iron may be due to random variation. In period 32—40 weeks all the blood characteristics are significantly lower than in the normal material.

The percentage deviation of the blood values during pregnancy is seen in diagram 2.

The curves for red cells and hematocrit lie close together during the first four periods and then spread apart; the hemoglobin curve lies markedly lower throughout. In period 24—32 weeks of gravidity the hematocrit and red cell values lie about 13 per cent lower than the corresponding values in the normal material; the hemoglobin lies about 18 per cent lower. The serum iron sustains the highest percentage diminution, or respectively 25 and 35 per cent in periods 24—32 weeks and 32—40 weeks. I would point out, however, that the drop from one of these periods to the next may be statistically random.

The curves for mean corpuscular hemoglobin concentration and mean corpuscular hemoglobin during the first 4 periods of pregnancy lie about 6 per cent below the normal material, and the former value remains on this level during the fifth period also. In that period the mean corpuscular hemoglobin drops another 4 per cent or so. During most of the gestational period the mean corpuscular volume remains normal, but in period 32—40 weeks it drops by about 5 per cent.

SUMMARY. — Early during pregnancy (period 6—16 weeks) the values for most of the blood characteristics lie significantly lower than in the normal material. Only for mean corpuscular volume and serum iron the differences may be due to random variation. Early pregnancy is therefore characterized by marked hypochromia, which may be observed in the 18 cases in the 6th—7th week of pregnancy. (At this time the difference between the mean corpuscular hemoglobin concentrations in the normal and the pregnant materials is 2.4 ± 0.34 , and consequently significant.)

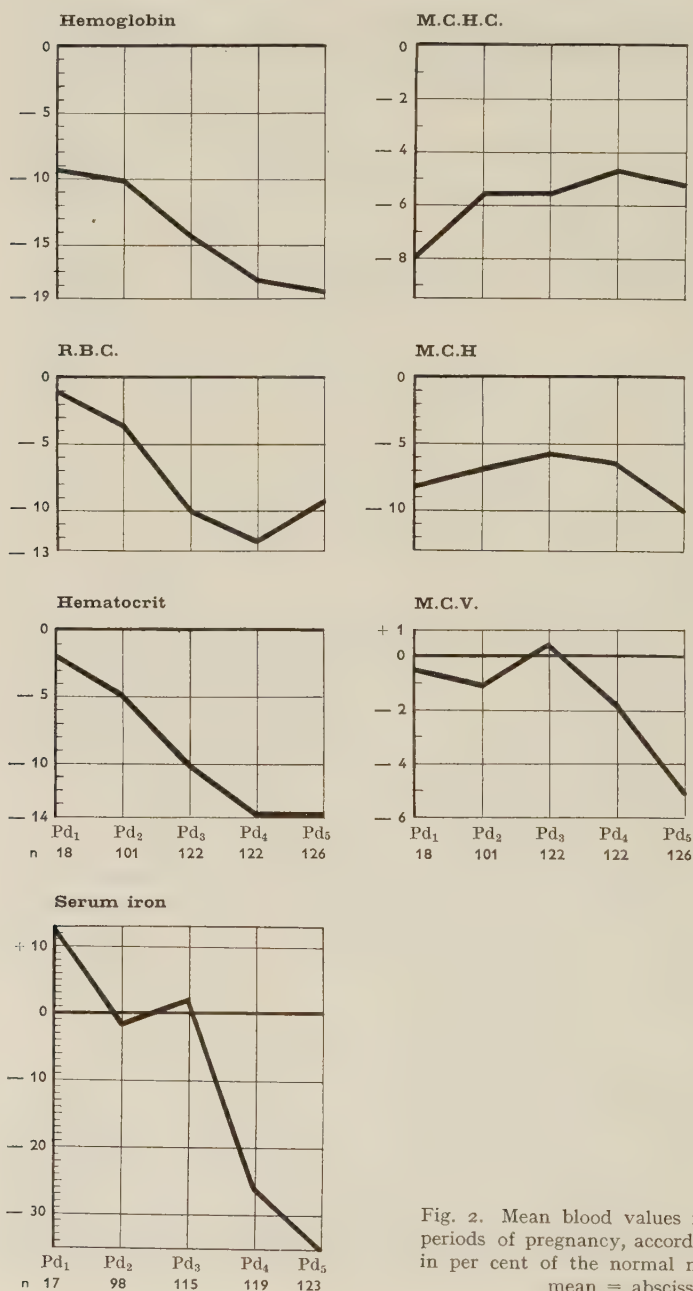


Fig. 2. Mean blood values in the different periods of pregnancy, according to table 10, in per cent of the normal means. Normal mean = abscissa.

In the last 8-week period of pregnancy all the mentioned blood characteristics are significantly lower than in the normal material, and in addition to the hypochromia moderate microcytosis has set in.

Changes of Blood Characteristics in the Different Periods of Pregnancy.

The formation of blood in the fetus commences as early as the first month of pregnancy, but at that time it naturally does not influence the maternal hemopoiesis. From this aspect any changes in her blood would most likely occur at the end of pregnancy. However, the problem is rendered more complex by hydremia which probably sets in fairly early in the gestational period.

Table 10 and diagram 1 suggest that the greatest change comes after the 2nd period of pregnancy (8th—16th week). In order better to illustrate the magnitude of the changes, we may combine period 1 with period 2 and period 3 with period 4. The 5th period, which apparently is characterized by certain changes in relation to all the rest of the material, may suitably be compared with the combined 2nd and 3rd periods.

Table 14 shows that from period 1+2 to period 3+4 all the blood characteristics investigated, except the corpuscular values, decrease significantly. The significant differences amount to between 3.6 (serum iron) and 9.8 (red cells) times their mean errors. From period 2+3 to period 5 the decrease is significant, except for mean corpuscular hemoglobin concentration and red corpuscles ($P \approx 0.2$). In this case the significant differences amount to between 5.6 and 11.6 times the respective mean errors. (Mean corpuscular hemoglobin concentration is not included in table 14 since it was discovered that throughout pregnancy the changes may be due to random variation.)

Table 14. *Differences and standard error of the differences between various periods in the main material (Abbreviations see table 10).*

Blood characteristics	Differences between			
	No.	Pd ₁ + Pd ₂ and Pd ₃ + Pd ₄	No.	Pd ₂ + Pd ₃ and Pd ₅
Hemoglobin (gm/100 cc blood)	363	0.74 ± 0.08	349	0.68 ± 0.10
Red cells (mill./c.mm)	363	0.330 ± 0.037	349	0.090 ± 0.038
Hematocrit (vol. per cent) ..	363	2.87 ± 0.29	349	2.41 ± 0.34
M.C.H. (γγ)	363	-0.28 ± 0.21	349	1.14 ± 0.20
M.C.V. (c.μ)	363	-0.33 ± 0.72	349	4.30 ± 0.68
Serum iron (γ/100 cc)	349	16.2 ± 4.4	336	45.4 ± 3.9

Table 15. *Probability (P) on comparison between different periods in the main material. (Abbreviations see table 10.)*

Blood characteristics	P values on comparison between			
	Pd ₁ and Pd ₂	Pd ₂ and Pd ₃	Pd ₃ and Pd ₄	Pd ₄ and Pd ₅
Hemoglobin.....	>0.2	<0.001	0.001	>0.2
Red cells	0.2	<0.001	<0.01	≈0.001
Hematocrit	0.2—0.05	<0.001	<0.001	>0.2

Table 16. *Probability (P) on comparison between some periods in the main material.*

Corpuscular values	P values on comparison between	
	Pd ₁ , Pd ₂ , Pd ₃ and Pd ₄	Pd ₁ , Pd ₂ , Pd ₃ , Pd ₄ and Pd ₅
M.C.H.C.	—	0.2—0.05
M.C.H.	>0.2	<0.001
M.C.V.	≈0.2	<0.001

A more exact comparison between the periods of pregnancy is shown in tables 15 and 16. In order to save space, only the probability of the comparisons is given. A priori a positive correlation is probable between the blood values in a group observed on several occasions. Thus, if on a given occasion one blood value lies higher than another, it probably still does so after not too long a time, provided nothing special has occurred. It would therefore have been more correct to make the calculations with this tendency in view. The original intention, which was to observe each case in each of the five 8-week periods of pregnancy, could not be realized (see table 5), however, and it would therefore have been a very complicated procedure to take into account the correlation in the statistical analysis. The correlation being positive, the probability cannot have become higher in the comparisons. Since the differences evidently are statistically significant, I have chosen to make the comparisons, neglecting the correlation. Whenever (Chapters 7 and 8) the same groups were compared, the differences were naturally formed and tested according to the null hypothesis.

From period 0—8 weeks to period 8—16 weeks there are no consistent differences for the blood characteristics. Then the hemoglobin, red cell, and hematocrit values decrease significantly to period 16—24 weeks. This is also the case from these to period 24—32 weeks. From the latter period to full term, the hemoglobin and hematocrit values do not change, whereas the red cell count increases significantly. We note, thus, that the reduction in red cells between the 3rd and 4th period and the subsequent augmentation do not appear in table 14.

The mean corpuscular hemoglobin concentration does not vary significantly from period to period during pregnancy. Through the first 4 periods the differences seem to be random for mean corpuscular volume and mean corpuscular hemoglobin, but in the last period they both decrease significantly.

Between the first 3 periods of pregnancy within number of earlier deliveries the differences for the serum iron may be due to random variation ($P > 0.2$). Later there is a significant decrease ($P < 0.001$) but the decrease between the 4th and 5th period is not statistically probable. (If the variation from number of deliveries is not eliminated, the serum iron decrease becomes statistically probable, $P < 0.01$.)

Correlation and Regression in the Main Material during Pregnancy and in the Normal Material.

Obviously, the values discussed previously sometimes may be correlated more or less strongly. Therefore it is interesting to treat the material with a view to correlation. Some coefficients of regression and their interrelationships have also been studied.

Tables 17 and 18 show the value of some coefficients of correlation in the normal material and in various periods in the main material.

Table 17. Coefficient of correlation, r , and its standard error, $\varepsilon(r)$, for some blood characteristics in the normal material and 32th—40th weeks of pregnancy (Pd_5).

Correlation between	Number	Normal material	Number	Pd_5
		$r \pm \varepsilon(r)$		$r \pm \varepsilon(r)$
Hemoglobin — hematocrit ..	98	0.51 ± 0.074	126	0.86 ± 0.023
Hemoglobin — M.C.H.C.	98	0.52 ± 0.074	126	0.92 ± 0.014
Hemoglobin — M.C.V.	98	0.07 ± 0.101	126	0.23 ± 0.084
Hematocrit — M.C.V.	98	0.37 ± 0.087	126	0.55 ± 0.062

Table 18. Coefficient of correlation, r , between hematocrit and mean corpuscular volume in the different periods of the main material.

Period of pregnancy, weeks	Number	$r \pm \varepsilon(r)$
0—8	18	0.34 ± 0.208
8—16	101	0.18 ± 0.096
16—24	122	0.41 ± 0.076
24—32	122	0.55 ± 0.063
32—40	126	0.55 ± 0.062

Comparing the normal material with the main material in period 32—40 weeks, it appears that in the latter the coefficients of correlation consistently have a higher numerical value. This is most characteristic of the correlation between hemoglobin on the one hand and mean corpuscular hemoglobin concentration and hematocrit on the other, and between hematocrit value and mean corpuscular volume. The correlation between hemoglobin and mean corpuscular volume may be due to random variation both in the normal material and period 32—40 weeks.

A comparison between tables 17 and 18 shows that the correlation between the hematocrit value and mean corpuscular volume is uncertain in the first two periods of pregnancy, but that it becomes significant as from the 3rd period and that the numerical value of the coefficient of correlation increases.

The results of covariance analysis of the mean corpuscular hemoglobin concentration on hemoglobin in the normal and main materials are entered in table 19.¹

As expected, the means in the various periods and the normal material deviate significantly from the mean regression line within periods and normal material, but this gives no information in addition to that already obtained in this chapter. It is all the more interesting, however, that while the coefficients of regression of these blood characteristics in the normal material and the four first periods of pregnancy only differ at random, the differences between the coefficients become significant if period 32—40 weeks is included. The numerical value of the coefficients of regression in the normal material and the first four

¹ The sum of the squares in the dependent variable y may be subdivided as follows:

$$\sum_{i=1}^p \sum_{j=1}^{n_i} (y_{ij} - \bar{y})^2 = \sum_{i=1}^p \sum_{j=1}^{n_i} (y_{ij} - Y_{x_{ij}})^2 + \sum_{i=1}^p \sum_{j=1}^{n_i} (Y_{x_{ij}} - \bar{y})^2$$

where Y_x is the y -value on the regression line for different x -values, and $\bar{y}$ the mean. This subdivision, however, holds not only for the total sum of the squares but also for the partial sum of the squares "between" and "within". The first term in the right member, the residual square, is a measure of the sum of the square deviation from the regression line, whereas the second term is the regression part of the sum of squares. When there is more than one group, the residual square obtained from the sum of squares "within" is a measure of the deviation from the parallel regression lines within the groups. The difference between this residual square and the residual square which is a measure of the deviation from the regression lines in the individual groups, determines the probability of whether the coefficients of regression in the separate groups are equal.

Since the regression part of the sum of the square has one degree of freedom, the residual square will have a degree of freedom less than the sum of the squares in y . The mean residual square is the ratio between the residual square and its degree of freedom.

Table 19. *Analysis of covariance of mean corpuscular hemoglobin concentration on hemoglobin in the normal and the main material. (In this table "periods" includes the normal material, wherever applicable.) Abbreviations see table 10.*

Source of variation	Differences between					
	Normal material, Pd ₁ , Pd ₂ , Pd ₃ , and Pd ₄			Normal material, Pd ₁ , Pd ₂ , Pd ₃ , Pd ₄ , and Pd ₅		
	Degrees of freedom	Mean residual square	Ratio	Degrees of freedom	Mean residual square	Ratio
1. Total	459	36.6		585	30.5	
2. Mean values of the periods in relation to mean regression line within periods	4	470.4	470.4 ¹	5	341.1	341.1 ¹
3. Variates in relation to the parallel regression lines within periods (error) ...	455	32.8	32.8	580	27.8	27.8
4. Variates in relation to their own periodic regression lines	451	32.6		575	26.6	
Differences between 3 and 4	4	52.7	52.7 ²	5	502.9	502.9 ¹
			32.6			26.6

¹ $P < 0.001$.

² $P_{0.2} > P > 0.05$.

periods vary between 0.50 and 1.07, whereas the coefficient in period 32—40 weeks is 1.40.

A study of the covariance for hematocrit on hemoglobin shows random differences between the coefficients of regression in the normal material and all the periods of pregnancy ($0.2 > P > 0.05$.)

SUMMARY. — The correlation between hemoglobin, on the one hand, and hematocrit and mean corpuscular hemoglobin concentration, on the other, becomes stronger in the main material in the 5th period of pregnancy (32—40 weeks) than in the normal material. During pregnancy, correlation arises between hematocrit and mean corpuscular volume, but the normal material also shows a weak correlation.

The coefficients of regression for mean corpuscular hemoglobin concentration on hemoglobin shows random differences between the normal material and the first four 8-week periods of pregnancy, but the inclination of the regression line changes significantly and becomes steeper in the 5th period (32nd—40th week) of pregnancy.

Discussion.

Early in pregnancy (0—16 weeks) the erythroid elements in this material lie significantly lower than in the normal material. The lowest values are reached in period 24—32 weeks, the red cell and hematocrit values being only about 87 per cent of the corresponding values in the normal material. In the 32nd—40th week of pregnancy the red cell count increases significantly, whereas hemoglobin and hematocrit remain practically unchanged.

MEAN CORPUSCULAR HEMOGLOBIN CONCENTRATION DURING PREGNANCY. — The hemoglobin value throughout remains on a lower level than the other erythroid values in comparison to the normal material. Throughout pregnancy the mean corpuscular hemoglobin concentration differs significantly from the normal material: a sign of hypochromia. This condition remains constant all the time that examinations were made, i. e. from the 6th to the 40th week. In the present material the possibility of errors of measurement may be disregarded. Neither can seasonal hemoglobin variations, if any, be made responsible; the normal material was selected during the first months of the year, and in the main material the first examination took place in the first half of the year. Nor do any of the investigated sources of variation of either hemoglobin or mean corpuscular hemoglobin concentration indicate that the material was in any way heterogeneous. Probably, therefore, pregnancy entails a reduced synthesis of hemoglobin in relation to the stroma formation. Owing to our incomplete knowledge as to hemoglobin synthesis, the reason for the hypochromia is obscure.

Beside WOLFF and LIMARZI (1945), I have not found that any of the authors who have dealt with this subject have found a decrease during pregnancy of the mean corpuscular hemoglobin concentration. (BETHELL *et al.* (1939) indirectly make the same statement.) ESCH (1932) reported a finding of oligochromemia caused by pregnancy. OBERST and PLASS (1936), among others, found a marked increase during pregnancy and WATSON (1938) declared that the mean corpuscular hemoglobin concentration lay within normal limits, but he lacked a normal material and his values *may* very well be suggestive of hypochromia. The hypochromic tendency is traceable in the immense material reported in 1936 by ADAIR, DIECKMAN, and GRANT. Their figures show that the mean corpuscular hemoglobin concentration is more than 0.3 units lower in the pregnant material of 7,696 cases than in a material of 1,227 gynecologic cases. I have myself arrived at the figure 0.3 but had to do so on the basis of an unequal number of hematocrit and hemoglobin values. Another group of this material, with 155 "private" patients, had a mean corpuscular hemoglobin concentration which lay more than 0.6 units lower than in the gynecologic cases.

MEAN CORPUSCULAR VOLUME DURING PREGNANCY. — During the last 8 weeks of pregnancy the significant increase of the red cell count is accompanied by a significant decrease of the mean corpuscular volume. The moderate hypochromia discussed above has, consequently, become associated with moderate microcytosis. Of course, this could be so because a substantial part of the material had become strongly microcytic. But this is not the case, as the coefficients of variation of all the corpuscular values, especially in period 32—40 weeks, show good agreement with those in the normal material. Thus, the main material has undergone a fairly uniform change in the corpuscular values.

The morphologic background of this microcytosis must be briefly discussed. In "non-anemic" pregnant women the mean diameter of the blood corpuscle appears to be normal (BOYCOTT 1936, ELLIOTT 1944, HARJOLA 1946). Elliott, however, reports an increase in the coefficient of variation, but Boycott and Harjola have found this only in sideropenia. In anemia of pregnancy the diameter of the blood corpuscle goes down according to Boycott and Elliott.

As regards the mean corpuscular diameter, Harjola, on the other hand, found good agreement between his 10 normal cases and 42 pregnant women with "graver anemia." In his normal material, the colour index was on the average 0.97 and in the pregnant material 0.81. LUNDHOLM's material of hypochromic anemia with the colour index lower than 0.75 included 30 persons in pregnancy or post partum. In these the mean colour index was 0.58 and in 20 the mean corpuscular diameter was 6.9 ± 0.07 . In Lundholm's normal material, the colour index was 0.99, and in 32 of the cases the mean corpuscular diameter was 7.3 ± 0.02 .

In my main material, the mean corpuscular hemoglobin in weeks 32—40 lies 10 per cent lower than in the normal material. It is likely, therefore, that the main material has a higher mean colour index in the period mentioned than Harjola's material with "graver anemia." It also seems likely that, even if the mean corpuscular diameter in the main material is decreased in the 5th period, the decrease is negligible.

In pregnant anemic patients, Elliott found a significantly increased fragility of the red corpuscles associated with an increasing mean corpuscular average thickness. However, judging by the above, it is unlikely that the lowered mean corpuscular volume in my material in the 5th period is associated with spherocytosis. (Spherocytosis, further, is usually associated with normocytosis or macrocytosis.) In this case it seems likely that the microcytosis is an early symptom of so called iron deficiency anemia. Also, this microcytosis can apparently be prevented by administration of iron salt in adequate amounts (see Chapter 8).

The question of the relationship between mean volume and mean diameter of the red corpuscles in pregnancy should, however, be further

studied. In so doing special emphasis should be laid on the fragility of the red cells and, as far as possible, on their life span compared with non-pregnant materials.

SERUM IRON DURING PREGNANCY. — Approximately up to the 24th week of pregnancy, the serum iron level in the main material does not differ consistently from normal. Thus, the serum iron level deviates considerably from the other blood characteristics, all of which except the mean corpuscular volume in weeks 6—16 lie significantly lower than the corresponding values in the normal material. In addition, the hemoglobin, red cell and hematocrit levels decrease significantly after week 8—16. The serum iron decrease does not take place until week 18—24, but in return it is much more pronounced, i. e. 25—35 per cent. This marked difference between the changes of erythroid elements and serum iron in pregnancy must surely be related to the regulation and role of the serum iron, which is discussed briefly in chapter 1, p. 8. In pregnancy, the endocrine balance is altered and in the last trimester the iron requirements are in excess of normal. The comparatively high serum iron level in the first three 8-week periods of pregnancy can possibly be due to increased mobilization of depot iron. The subsequent marked decrease may conceivably be an effect of increased consumption, or of deficiency, or perhaps of a combination of both these factors.

The probably lower serum iron level, during pregnancy in women who have given birth to more than one child, may be interpreted as a lowered capacity to deliver iron, due to depletion of their iron depots.

I wish to stress, however, that the influence of age in this respect may have been greater than shown by the statistical analysis, but the tendency in multiparae older than 34 is the same as in younger multiparae. It therefore seems justified to assume that the most important source of variation is the ordinal number of the delivery. Naturally, it would have been interesting to investigate whether closely spaced pregnancies could have affected the serum iron value, but the material is too small for an investigation of this type.

WHY THE BLOOD CHARACTERISTICS ARE LOWERED DURING PREGNANCY. — During pregnancy the blood characteristics decrease and the blood picture undergoes microcytic and hypochromic changes. First and foremost, this apparently is due to dilution of the blood, so that the production of red blood corpuscles cannot keep up with the dilution. The second reason seems to be a change in the erythropoiesis, due either to deficiency or altered function. So far, it is difficult to distinguish between these reasons, but some available facts may be helpful.

According to MACARTHUR (1948) "Protein and hematocrit levels expressed in terms of percentage are practically identical throughout pregnancy". The protein concentration in the plasma is also a measure of

the dilution: the less protein, the more water per unit volume of blood (NAESLUND 1931, OBERST and PLASS 1936). Dilution, provided changes are solely due to this factor, would have reduced the hematocrit value in this material by 13 per cent approximately. Such a reduction takes place in period 24—32 weeks, while in the preceding period the corresponding figure is 10 per cent.

The rapid lowering of the blood values during the first half of pregnancy may be an effect of dilution. In the later stages of pregnancy, when the dilution has been in effect for some time and the demands on the maternal depots of, for example, iron (fetus, uterus, placenta) have increased, there will probably be a deficiency. The serum iron level and a moderate but significant lowering of the mean corpuscular volume may be a sign hereof. The already existing hypochromia, however, does not become accentuated.

The fact that a deficiency does actually arise toward the end of pregnancy is borne out by several observations. Thus, Markhoff (1938) and Wolff and Limarzi (1945) have found that during the later stages of pregnancy the bone marrow changes are most marked. Wintrobe (1934) has on the basis of a large anemic material shown that in hypochromic microcytic anemia the correlation is close between hemoglobin on the one hand and mean corpuscular hemoglobin concentration (0.8390 ± 0.0109) and mean corpuscular volume on the other. The coefficient of regression for corpuscular hemoglobin concentration on hemoglobin was ($n = 347$) 1.04. In my material there is no significant correlation between hemoglobin and corpuscular volume, not even in period 32—40 weeks. (The coefficient of correlation is numerically much higher than in the normal material and fairly close to a value where the correlation would be significant.) The coefficient of correlation in the latter period between hemoglobin and corpuscular hemoglobin concentration was very close, or 0.92. Furthermore, the existing and increasing correlation between hematocrit value and mean corpuscular volume during pregnancy indicates a change in the material. The significantly higher coefficient for the regression of the mean corpuscular hemoglobin concentration on hemoglobin in period 32—40 weeks is also a strong factor in support hereof. It should be noted that this change in the regression coefficients sets in, although the hemoglobin and hematocrit values do not alter much from the 4th to the 5th period. *All these changes, which probably have developed gradually but are most strongly manifested in the last 8 weeks of pregnancy, strongly suggest as stated previously, that a biological change affects the material uniformly. It is reasonable to assume that the significance of the observed changes indicates a tendency in the material towards anemia, and the reason is a deficient condition, with iron deficiency as the most tangible factor.*

If the anemization is due to iron deficiency, it seems likely that administration of large doses of iron in the early stages of pregnancy would

have little or no effect on the blood characteristics, except possibly hemoglobin. Similar medication during the later stages of pregnancy, and especially during the last 8 weeks, would by the same token yield results parallel to iron administration in microcytic, hypochromic anemia in non-pregnant subjects. In a later chapter I shall describe some experiments to test this assumption and their results.

CAN THE SYMPTOMS OF ANEMIA AT THE END OF PREGNANCY BE DUE TO LATENT ANEMIA PREEXISTENT TO PREGNANCY? — FULLERTON (1936), STURGIS (1941), and others assume that anemia of pregnancy usually is preexistent. As the anemic changes attack my material uniformly, I shall briefly discuss this question.

Researches by ODIN (1934), LUNDHOLM (1939), and WALDENSTRÖM (1946) may indicate that some Swedish provinces exhibit notably higher frequencies of so called iron deficiency anemia than the rest of the country. However, Waldenström's investigation of different groups from Uppland (where my investigations were carried out) makes it probable that this form of anemia is common chiefly in certain country districts with special dietic habits that result in a lack of animal proteins (meat). In Enghoff's material of 1937, there were no remarkable differences between Uppsala and Lund (South Sweden) in the blood characteristics of normal materials from these places.

In the main material, the diet seems to have been adequate. Only differences that may be due to random variation appear between various income classes and between groups that perhaps had had different dietic habits. During the first half of pregnancy as well as in the normal material, the serum iron, moreover, lies at a normal level, provided that multiparae are excluded.

From this it is evident that my material of pregnant women very likely does not come from an anemic population or a population with latent anemia, and it should therefore be justifiable to assume that, in my material, a deficient condition existing prior to pregnancy cannot have caused the changes in the last stages of pregnancy.

INCIDENCE OF ANEMIA DURING PREGNANCY. — A problem of considerable practical importance is where the lower limit should be drawn for the normal variation of the blood characteristics during pregnancy. On the basis of the present material, I cannot with certainty express any opinion on this subject. The patients lack subjective symptoms of anemia, and the changes taking place up to the 32nd week of pregnancy may, as explained earlier, be attributed to hydremia, even if there is hypochromia during the early stages. The erythroid elements which in the latter half of pregnancy lie about 10 per cent lower than in a normal material should not right away be considered pathologic. In weeks 16–24 the mean hematocrit value was 35.2 vol. per cent. A limit for normal variation, arbitrarily fixed at twice the standard deviation on either side of the mean, could give a lower value of about 29.5 per

cent, and therefore a value as low as this needs not necessarily be pathologic. (Cf. Chapter I for incidence of anemia in other materials.)

Thus, the importance of the numerical magnitude of the blood characteristics should not be overestimated. The essential thing is that during the last 8 weeks of pregnancy the material has changed uniformly, so that symptoms of microcytic anemia are added to symptoms of hypochromia.

DIET AND ANEMIA IN PREGNANCY. — As mentioned above, all the test persons had probably been on an adequate diet, and none of them was markedly undernourished. Papers dealing with these problems contain widely different opinions as to the importance of the diet for the development of anemia in pregnancy.

STRAUSS and CASTLE (1932) expressed the opinion that iron deficiency in the food plays an important part in the genesis of hypochromic, microcytic anemia during pregnancy, and in 1933 they emphasized that protein deficiency may cause anemia of macrocytic type. Repeatedly and most recently in 1943, BETHELL *et al.* have on the basis of large test series considered themselves able to prove the same thing, hypochromic, microcytic anemia developing only in subjects with a daily supply of food iron of 12—15 mg or less. TOVERUD (1935), EBBS (1941), and TITUS (1946), among others, have stressed the correlation between a diet poor in iron and the incidence of anemia in pregnancy. DIECKMANN *et al.* (1944) found no difference in the blood values between groups that had been put on different diets, even if some groups had been given iron salts. TALSO and DIECKMANN (1948) did not even observe any improvement in cases of microcytic anemia during pregnancy (cf. p. 18).

In this material I have separated the test persons into two groups with annual incomes over or below the arbitrary figure 6,000 kronor. The group with annual incomes of 6,000 kronor or more probably includes families in comfortable circumstances whose diet was high in vitamins, proteins and perhaps iron, as compared with families with a lower annual income than 6,000 kronor. (The latter group also includes all the unmarried women in the material.) The classification into urban and rural domicile is chiefly a matter of dietic habits. The number of rural cases was small and the difference in dietic habits between Uppsala and the surrounding countryside can probably be important only in special circumstances. As has been shown earlier none of these classifications yielded either probable or significant differences. Judging by the dietic cases histories, this result could perhaps a priori have been foreseen, and, probably, differences in the blood characteristics could have been obtained only by comparing groups with highly different economic conditions (one of the groups being extremely poor).

In a small number of cases the subjects had for various reasons avoided certain foods. Thus, for example, 9 women would take no milk and

had thereby missed proteins of high biologic value. The blood values of these women in the 32nd—40th week of pregnancy differ but little from the means in table 10, and the same is the case with 8 other women who only ate negligible amounts of animal proteins, but their mean corpuscular volume is 3 units lower.

A reduced absorption of iron and other substances may be due to lack of appetite or comparatively severe disorders of the gastro-intestinal tract. The 20 cases with emesis gravidarum lasting more than 2 months and the 7 with fairly grave gastro-intestinal disorders do not measurably deviate as regards blood characteristics from the cases in table 10 during weeks 32—40.

SIDEROPENIC SYMPTOMS IN THE MATERIAL. — During pregnancy there were no subjective symptoms of anemia that could not be attributed to some other more likely reason. None of the changes in tongue and nails characteristic of sideropenia were seen with certainty. Only 16 persons had tongue and nail changes with low papillae and thin brittle nails. In weeks 32—40 of pregnancy the hemoglobin and hematocrit values of these test persons did not deviate from the means given in table 10.

CHAPTER 6.

Blood Characteristics in the Main Material during Labour and Puerperium.

Table 20 and diagram 3 show the changes in the blood characteristics in the main material during labour and puerperium. Hemorrhage classes over 600 cc have been grouped together.

For the sake of comparison, the blood values for the last 10 weeks of pregnancy are also given. (These differ but little from the 5th period [weeks 32—40] of pregnancy.) From the table and the diagram it appears that in general the blood values show an increase from the period 30th—40th week; the exceptions are the mean corpuscular hemoglobin concentration and the mean corpuscular hemoglobin and serum iron. About 6 weeks post partum, however, they still lie far below the level of the normal blood characteristics.

The hemorrhage in connection with delivery is recorded in table 21. One patient was delivered through cesarian section. Therefore the hemorrhage was uncertain and I approximated it to about 1,000 cc. The median of the hemorrhage is 393 cc, the lower quartile 268 and the upper 611 cc.

As regards complications during the puerperium see Chapter 3.

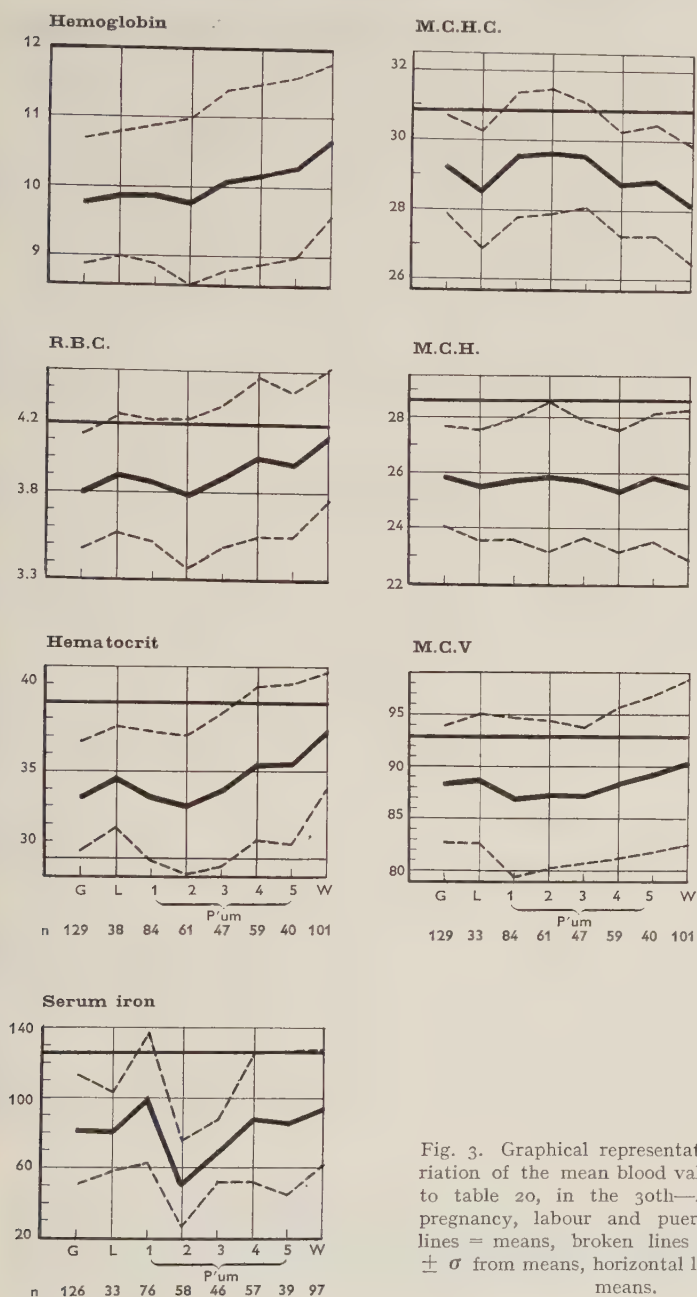


Table 20. *Mean blood values of the main material in*

Intrapartum haemorrhage in cc: I = 0—300 cc.

II = 300—600 cc.

III = 600— cc.

Blood characteristics	Haemorrh. class	G. 30th—40th w. of pregn., average 35 w.		L. During labour		P ^{um} ₁ . 1st—2nd ¹ day after delivery		P ^{um} ₂ . 3rd—4th day after delivery	
		No.	M ± ε (M)	No.	M ± ε (M)	No.	M ± ε (M)	No.	M ± ε (M)
Hemoglobin (gm/100 cc blood)	I	—	—	—	—	26	10.1	19	10.4
	II	—	—	—	—	38	10.1	25	10.0
	III	—	—	—	—	20	9.4	17	8.8
	Total	129	9.8 ± 0.08	33	9.9 ± 0.16	84	9.9 ± 0.11	61	9.8 ± 0.15
Red cells (mill./c.mm)	I	—	—	—	—	26	3.98	19	4.05
	II	—	—	—	—	38	3.94	25	3.85
	III	—	—	—	—	20	3.57	17	3.43
	Total	129	3.81 ± 0.03	33	3.91 ± 0.06	84	3.87 ± 0.04	61	3.80 ± 0.06
Hematocrit (vol. per cent)	I	—	—	—	—	26	35.1	19	35.4
	II	—	—	—	—	38	34.0	25	33.6
	III	—	—	—	—	20	31.1	17	29.7
	Total	129	33.6 ± 0.27	33	34.7 ± 0.50	84	33.6 ± 0.41	61	33.1 ± 0.51
M.C.H.C. (per cent)	I	—	—	—	—	26	28.8	19	29.5
	II	—	—	—	—	38	29.9	25	29.8
	III	—	—	—	—	20	30.2	17	29.6
	Total	129	29.3 ± 0.12	33	28.6 ± 0.29	84	29.6 ± 0.20	61	29.7 ± 0.23
M.C.H. (γγ)	I	—	—	—	—	26	25.4	19	25.7
	II	—	—	—	—	38	25.8	25	26.2
	III	—	—	—	—	20	26.2	17	25.7
	Total	129	25.9 ± 0.15	33	25.6 ± 0.34	84	25.8 ± 0.24	61	25.9 ± 0.34
M.C.V. (c.μ)	I	—	—	—	—	26	88.4	19	87.7
	II	—	—	—	—	38	86.2	25	87.7
	III	—	—	—	—	20	87.2	17	86.6
	Total	129	88.4 ± 0.50	33	88.9 ± 1.07	84	87.1 ± 0.83	61	87.4 ± 0.90
Serum iron (γ/100 cc)	I	—	—	—	—	23	106.8	19	85.2
	II	—	—	—	—	35	103.9	22	77.9
	III	—	—	—	—	18	88.4	17	64.4
	Total	126	82.6 ± 2.7	33	81.1 ± 3.9	76	100.4 ± 4.3	58	76.3 ± 3.2

¹ 1st day after delivery = day of birth.

For the sake of comparison, the blood characteristics for the period 30th—40th week and the values actually taken during the labour were grouped according to hemorrhage classes. From this it appeared that the probability (P) in the comparisons between the four hemorrhage

30th—40th week of pregnancy, labour and puerperium.

Hemorrh. class	P'um ₃ . 5th—6th day after delivery		P'um ₄ . 7th—8th day after delivery		P'um ₅ . 9th—10th day after delivery		W. About 6 w. post partum— range 3—13 w. ²	
	No.	$M \pm \varepsilon (M)$	No.	$M \pm \varepsilon (M)$	No.	$M \pm \varepsilon (M)$	No.	$M \pm \varepsilon (M)$
I	9	10.9	19	10.9	10	10.8	35	10.8
II	25	10.3	22	10.2	18	10.7	44	10.7
III	13	9.0	18	9.5	12	9.1	22	9.8
Total	47	10.1 ± 0.19	59	10.2 ± 0.17	40	10.3 ± 0.21	101	10.6 ± 0.11
I	9	4.16	19	4.36	10	4.11	35	4.24
II	25	4.00	22	3.96	18	4.13	44	4.13
III	13	3.53	18	3.70	12	3.60	22	4.01
Total	47	3.90 ± 0.06	59	4.01 ± 0.06	40	3.97 ± 0.07	101	4.14 ± 0.04
I	9	37.9	19	38.5	10	38.0	35	38.4
II	25	34.7	22	35.3	18	36.9	44	37.5
III	13	30.1	18	32.4	12	31.3	22	35.3
Total	47	34.0 ± 0.64	59	35.5 ± 0.58	40	35.5 ± 0.73	101	37.4 ± 0.34
I	9	28.9	19	28.2	10	28.4	35	28.2
II	25	29.7	22	28.9	18	28.9	44	28.3
III	13	29.8	18	29.2	12	29.2	22	28.0
Total	47	29.6 ± 0.22	59	28.8 ± 0.20	40	28.9 ± 0.26	101	28.2 ± 0.17
I	9	26.3	19	25.0	10	26.4	35	25.7
II	25	25.9	22	25.8	18	25.9	44	26.0
III	13	25.4	18	25.5	12	25.3	22	24.7
Total	47	25.8 ± 0.31	59	25.4 ± 0.28	40	25.9 ± 0.36	101	25.6 ± 0.27
I	9	91.2	19	88.6	10	92.5	35	91.2
II	25	87.1	22	89.1	18	89.6	44	90.6
III	13	85.1	18	87.5	12	86.8	22	87.3
Total	47	87.3 ± 0.96	59	85.5 ± 0.94	40	89.4 ± 1.18	101	90.5 ± 0.79
I	9	79.2	18	120.6	10	116.0	34	111.4
II	24	71.6	22	78.6	17	86.1	41	96.5
III	13	60.5	17	68.5	12	62.0	22	70.9
Total	46	69.9 ± 2.6	57	88.8 ± 5.0	39	86.3 ± 6.5	97	95.2 ± 3.4

² In 87 cases 5—7 weeks.

classes in 9 of the 14 comparisons was about 0.2 or more for all the blood characteristics of interest here. In three cases, $0.2 > P > 0.05$, and in one case P was negligibly lower than 0.05. For the mean corpuscular hemoglobin concentration P reached the value 0.01. It should

Table 21. *Hemorrhage connected with delivery in the main material.*

Haemorrhage classes in cc.	No.	Mean haemorrhage
0—300.....	41	175
300—600.....	61	425
600—900.....	24	750
900 and more, range		
900—1350	10	—

be noted, however, that the mean square between the hemorrhage classes is lower than within the classes for all the 14 comparisons. Therefore it should be justifiable to compare the means both in the period 30th—40th week and during labour with any of the hemorrhage classes in the puerperium. It should also be noted that there are no significant differences in the blood values between the period 30th—40th week of pregnancy and the period of labour.

The intrapartum hemorrhage may be expected to be of great importance for the blood characteristics. This I shall show later. To get some idea of the variation of the blood values in cases, where the hemorrhage is of no major importance, we shall compare the blood characteristics during the last 10 weeks of pregnancy and in the normal material with the corresponding values on different occasions during the puerperium. The figures are given in tables 22 and 23 and diagram 4. It should be noted that these comparisons refer only to the intrapartum hemorrhage class 0—300 cc.

Between the period 30th—40th week of pregnancy and the 1st—2nd day of the puerperium (hemorrhage group 0—300 cc) the differences may be due to random variation, except for the significant serum iron increase. From the period 30th—40th week of pregnancy to about one week post partum the erythroid elements, the hematocrit value and the serum iron have increased significantly. The mean corpuscular hemoglobin concentration shows a significant decrease but the other corpuscular values have changed only in a random manner. (It should be noted that if the mean corpuscular hemoglobin concentration in all the classes combined on the 7th—10th day after delivery is compared with the 30th—40th week, the difference will be only 0.47 ± 0.20 (which corresponds to a $P \approx 0.02$).)

Between the period 30th—40th week of pregnancy and the period about 6 weeks after delivery (hemorrhage class 0—300 cc) the increase is significant for the erythroid elements, hematocrit value and serum iron. The mean corpuscular hemoglobin concentration has dropped significantly but the mean corpuscular hemoglobin value is almost unchanged. The increase of the mean corpuscular volume is not statistically probable but P is very close to 0.01.

Table 22. *Differences and P-values on comparison between different periods during puerperium (only haemorrhage class 0—300 cc) and 30—40 weeks during pregnancy (G) in the main material. (Abbreviations see table 20).*

$D \pm \varepsilon (D)$ = differences $\pm$ standard error of the differences.

Blood characteristics	No.	$D \pm \varepsilon (D)$	P
<i>Diff.: P'um₁ and G.</i>			
Hemoglobin.....	155	0.28 ± 0.21	>0.2
Red cells.....	155	0.17 ± 0.070	$0.02-0.01$
Hematocrit.....	155	1.47 ± 0.77	$0.2-0.05$
M.C.H.C.....	155	-0.48 ± 0.41	>0.2
M.C.H.....	155	-0.44 ± 0.52	>0.2
M.C.V.....	155	0.03 ± 1.76	>0.2
Serum iron.....	149	24.3 ± 7.9	$0.01-0.001$
<i>Diff.: P'um₄ + P'um₅ and G.</i>			
Hemoglobin.....	158	1.04 ± 0.23	<0.001
Red cells.....	158	0.46 ± 0.085	<0.001
Hematocrit.....	158	4.72 ± 0.80	<0.001
M.C.H.C.....	158	-0.96 ± 0.28	<0.001
M.C.H.....	158	-0.42 ± 0.40	>0.2
M.C.V.....	158	1.52 ± 1.36	>0.2
Serum iron.....	154	36.4 ± 9.5	<0.001
<i>Diff.: About 6 weeks post partum and G.</i>			
Hemoglobin.....	164	1.02 ± 0.18	<0.001
Red cells.....	164	0.43 ± 0.064	<0.001
Hematocrit.....	164	4.79 ± 0.58	<0.001
M.C.H.C.....	164	-1.07 ± 0.27	<0.001
M.C.H.....	164	-0.22 ± 0.42	>0.2
M.C.V.....	164	2.84 ± 1.29	$0.05-0.01$
Serum iron.....	160	28.9 ± 6.2	<0.001

Table 23. *Differences and standard error of the differences between normal material and the main material about 6 weeks post partum.*

Blood characteristics	No.	Differences between normal material and about 6 weeks post partum	P
Hemoglobin (gm/100 cc blood).....	133	1.19 ± 0.18	<0.001
Red cells (mill./c.mm).....	133	-0.040 ± 0.063	>0.2
Hematocrit (vol. per cent).....	133	0.57 ± 0.55	>0.2
M.C.H.C. (per cent).....	133	2.71 ± 0.28	<0.001
M.C.H. ($\gamma\gamma$).....	133	3.05 ± 0.43	<0.001
M.C.V. (c. μ).....	133	1.79 ± 1.30	$0.2-0.05$
Serum iron (γ /100 cc).....	131	15.4 ± 6.5	≈ 0.02

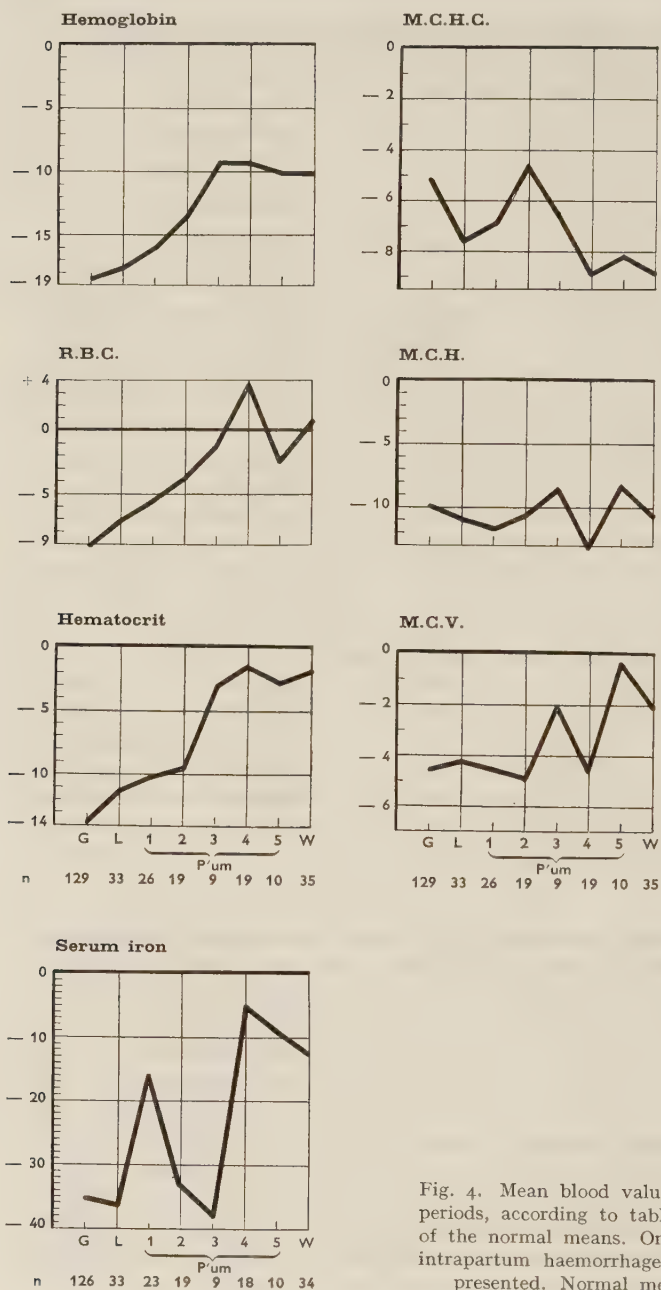


Fig. 4. Mean blood values in the different periods, according to table 20, in per cent of the normal means. Only the group with intrapartum haemorrhage 0—300 cc. is represented. Normal mean = abscissa.

As regards the comparison between the normal material and the main material in the period about 6 weeks after delivery (hemorrhage class 0—300 cc), the hemoglobin as well as the mean corpuscular hemoglobin and the mean corpuscular hemoglobin concentration lie significantly lower, but the discrepancies in the other blood characteristics may be a result of random variation.

In order further to illuminate the effect of the quantity of blood lost and the variation of the blood characteristics during the puerperium table 24 was constructed. The comparison is carried out simultaneously between all the periods as from the 1st and 2nd day after parturition up to and including the period about 6 weeks after delivery, but unlike table 20 the subdivision into 4 hemorrhage classes is maintained as in table 21.

The amount of blood lost can be expected to affect the blood values and this is corroborated by the statistical analysis. However, the differences found between the hemorrhage classes do not apply to the corpuscular values, of which the changes may be an effect of random variation.

Table 24 also shows that between all the periods (within hemorrhage classes) the differences are significant for red cells, hematocrit and serum iron as well as for the mean corpuscular hemoglobin concentration. For hemoglobin the differences are probable but for mean corpuscular hemoglobin and mean corpuscular volume they may be random.

The variation of the serum iron during the first 10 days after delivery is considerable. It would seem as though its level immediately after parturition, which in the two lowest hemorrhage classes is significantly higher than at the end of pregnancy, rapidly drops only to again rise significantly, at least in the hemorrhage class 0—300 cc.

SUMMARY. — The statistical analysis of the postparturient blood characteristics, and these values related to the period 30th—40th week of pregnancy and to the normal material, shows the following:

If only those blood groups are considered where the intrapartum hemorrhage did not amount to 300 cc, the erythroid elements and the hematocrit value show an increase from the period 30th—40th week of pregnancy to the examination about 6 weeks after delivery, the increase being significant already about one week after delivery. Serum iron also increases, but here there is wide variation a few days after delivery. These variations seem to show that very soon after parturition there is an increase which is quickly followed by a reduction. About one week after delivery the serum iron value again increases, at least if the hemorrhage associated with delivery had not amounted to 300 cc. The mean corpuscular hemoglobin changes but little, whereas the mean corpuscular hemoglobin concentration will be significantly lower at the examination about 6 weeks after delivery. This decrease is likely to be real already about one week post partum. The numerical

Table 24. *Analysis of variance of the material post partum with regard to hemorrhage and periods during puerperium. (Between or within »all periods« = between or within P'um₁, P'um₂, P'um₃, P'um₄, P'um₅, and W. The meaning of the abbreviations appears from table 20. Estimate of significance always made within periods or hemorrhage classes.)*

Blood characteristics (Class interval)	Source of variation	Degrees of freedom	Mean square	P
<i>Total for Hb, R.B.C., etc.:</i>		391		
Hemoglobin (0.2 gm/100 cc blood)	Within periods or hemorrhage classes (error)	368	27.3	
	Between all periods	20	54.0	≈0.01
	Between hemorrh. classes	18	178.7	<0.001
Red cells (0.06 mill./c.mm)	Within periods or hemorrhage classes (error)	368	33.5	
	Between all periods	20	119.9	<0.001
	Between hemorrh. classes	18	265.5	<0.001
Hematocrit (0.5 per cent)	Within periods or hemorrhage classes (error)	368	46.5	
	Between all periods	20	235.7	<0.001
	Between hemorrh. classes	18	408.0	<0.001
M.C.H.C. (0.25 per cent)	Within periods or hemorrhage classes (error)	368	44.2	
	Between all periods	20	156.6	<0.001
	Between hemorrh. classes	18	71.2	≈0.05
M.C.H. (0.25 γγ)	Within periods or hemorrhage classes (error)	368	94.1	
	Between all periods	20	48.1	0.05—0.01
	Between hemorrh. classes	18	62.6	0.2 —0.05
M.C.V. (1.0 c.μ)	Within periods or hemorrhage classes (error)	368	56.9	
	Between all periods	20	47.4	>0.2
	Between hemorrh. classes	18	39.2	≈0.2
<i>Total:</i>		372		
Serum iron (5.0 γ/100 cc. blood)	Within periods or hemorrhage classes (error)	349	37.6	
	Between all periods	20	104.4	<0.001
	Between hemorrh. classes	18	166.6	<0.001

increase of the mean corpuscular volume does not quite attain statistical probability.

About 6 weeks after delivery, the red cell and hematocrit count have risen so that the differences from the normal material are statistically random (hemorrhage class 0—300 cc). At this time the hemoglobin value on the other hand lies far below that of the normal material,

and the same thing applies to the mean corpuscular hemoglobin and the mean corpuscular hemoglobin concentration. The mean corpuscular volume and the serum iron value lie lower than in the normal material, but the differences may be effects of random variation.

The volume of blood lost during delivery strongly affects the blood characteristics except the corpuscular values. The affected blood values become lower as the hemorrhage increases.

Discussion.

Tables 20 and 24 unequivocally show how vastly important for the blood characteristics is the intrapartum hemorrhage. The greater the hemorrhage, the lower will be the erythroid elements and the serum iron. The corpuscular values, however, remain unaffected by the volume of the hemorrhage.

Several authors have considered the anteparturient hemoglobin value to be of importance for the frequency of complications at delivery and in the puerperium. SCHRUMPF (1930), for example, has maintained that the intrapartum hemorrhage is related to this value. Such an assumption is contradicted by the present material since in it the anteparturient blood characteristics, classified according to the intrapartum hemorrhage, were much the same. Moreover, the complications in the material were comparatively few and unimportant despite clearly lower blood values than in the normal material and other changes of an anemic nature, but none of my subjects showed excessively low blood values.

In the previous chapters I have, with the aid of my own material and that of other investigators, attempted to show that the reduction of the blood values during pregnancy is chiefly due to two factors: dilution and deficiency, most likely of iron, the latter causing anemic symptoms. Earlier investigators have rendered it probable that the augmentation of the blood volume taking place during pregnancy, the greater part of which probably is due to an increase in the plasma volume, quickly approaches the normal value after parturition. Possibly this decrease starts before full term.

In my material, when the intrapartum hemorrhage did not exceed 300 cc, the blood values rapidly increased after parturition. More than anything else this suggests a reduction in the volume of plasma, chiefly because the blood values increase quickly after a period of about 16 weeks with unchanged hemoglobin and hematocrit values. The unchanged corpuscular values may perhaps also be regarded as an indication that the dilution is receding.

Between one and about 6 weeks after delivery the blood values change extremely little (if cases with an intrapartum hemorrhage exceeding 600 cc are disregarded), but about 6 weeks after delivery the diminu-

tion of the mean corpuscular hemoglobin concentration was still more pronounced. It is probable that the deficiency, most likely of iron, that was evident at the end of pregnancy is now still more accentuated, presumably almost wholly because of the intrapartum hemorrhage. This is manifested by a more pronounced hypochromia than during pregnancy and the slow regeneration of the blood. In comparison the regeneration of blood in blood donors is considerably more rapid (Sköld and Walldenström 1940) and their serum iron usually remains normal despite heavy blood losses.

During the first few days after delivery the serum iron value varies within wide limits. If the values on the day of delivery (but after parturition) and the day after are combined there is an increase in comparison both with the period 30th—40th week of pregnancy and with the period during labour, and in the two lower hemorrhage classes this increase is significant. After that the value drops, only again to go up significantly in the lowest hemorrhage class. This result is incompatible with earlier investigations. The regular diminution of the serum iron value immediately after parturition cannot be observed in this material, though only the values for the day of delivery are considered. Heilmeyer and Plötner (1937), (SKOUGE 1939), reported a marked serum iron increase 24—48 hours after an initial decrease on a blood loss of 500—800 cc. In one of their cases serum iron value before venesection was 36 γ per cent. They tried to explain this mechanism as a mobilization of depot iron and the subsequent reduction of the serum iron value as a sign of rapid regeneration of blood. I agree with this explanation. Inability to mobilize sufficient depot iron may be the reason why the cases in the present material did not exhibit even higher serum iron values (cf. Heilmeyer and Plötner) immediately following parturition.

These changes in the blood after delivery explain why different authors have interpreted them so variously: the only blood characteristics that are different from the normal material about one week after parturition and later (in this case about 6 weeks after delivery) are hemoglobin, corpuscular values, where hemoglobin is one variable, and serum iron. (As elsewhere I disregard the hemorrhage classes above 300 cc.) Since materials that have been kept under observation after parturition have been small, the corpuscular values seldom studied, and systematic studies of the serum iron after pregnancy do not exist, it is natural that opinions differ greatly concerning the behaviour of the blood characteristics after parturition. However, as pointed out earlier, Kühnel and other authors have strongly emphasized the lag of the hemoglobin value.

It is clear from what has been said that, even in the most favourable cases, some anemization of the organism must still be expected about 6 weeks after delivery.

CHAPTER 7.

Blood Characteristics Some Months After Delivery.

Effect of Iron Treatment.

In Chapter 6 I reviewed the variation of the blood characteristics during and after labour, showing that even in the most favourable cases the test subjects had moderate hypochromia about 6 weeks after parturition. In order to study the duration of this condition some test persons were examined 3—8 months after delivery.

The material includes 44 subjects, of whom 41 belonged to the main material. The other 3 persons had originally been excluded from the main material; 2 owing to gestosis and 1 because the child at birth weighed merely 1,300 gm. During the first fortnight of 1948 we summoned all the mothers who originally had belonged to the main material and whose child had been born at least 3 months earlier. Unfortunately only 44 responded to the summons. As from the first examination (of those who came in answer to the summons) all the patients were perorally given bivalent, organic iron salt (ferrous tartrate). They were reexamined after about 1 month and had then taken about 10 gm. of iron.

The material is reviewed in table 25. It will be noted that the cases were subdivided into 3 classes with respect to their hemoglobin values at this examination some months after delivery. Both before and after this occasion the cases were put in the same class. Few persons only belong to the lowest class. However, it is probably justifiable to say that they have anemia, and therefore the class has been retained, so

Table 25. *Survey of the material (44 subjects) determined some month post partum with regard to hemoglobin quantity, number of earlier deliveries and intrapartum hemorrhage.*

Hemoglobin class in gm/100 cc. blood some month post partum	Month post partum			Number of earlier deliveries			Average hemorrhage at delivery. Range within brackets
	3—4	5—6	7—8	0	1	> 1	
8.35—9.87	3	2	0	2	1	2	620 (225—1350)
9.87—11.39	8	9	0	9	5	3	360 (75—800)
11.39—12.91	7	11	4	12	9	1	510 (150—850)
Total	18	22	4	23	15	6	—

that it may be compared with the other classes before and after pregnancy. These 5 cases are of microcytic and hypochromic type at the period some months post partum. In one of the cases, however, the mean corpuscular volume is 85 c. μ . and in only 3 of them the mean corpuscular hemoglobin concentration lies at 27 per cent or lower. The serum iron value in 3 of the cases lies below 60 γ per cent, and in 2 it is respectively 83 and 71 γ per cent.

In the lowest class none of the patients had been given iron before. In the middle class, 2 patients were given iron during pregnancy, one for about 1 month and the other during most of her pregnancy. In the same group, 2 received a small amount of iron during the puerperium, and yet another patient was given about 10 gm. of iron during the first month after delivery.

In the highest class one patient was medicated with iron for one month during pregnancy, one was given 2 gm. of iron during the puerperium and 3 took about 10 gm. of iron each during the month immediately following delivery.

During labour and puerperium this material exhibited the following complications:

The two largest hemorrhages occurred in the lowest class, one being of 1,350 and one of 990 cc. If these two largest hemorrhages are neglected the mean hemorrhage was only 355 cc.

In the middle class there were 6 slight cases of intrapartum albuminuria, 2 mild cases of puerperal endometritis, and 1 case of afebrile acute cystitis.

In the highest class there were 6 mild cases of intrapartum albuminuria, 2 cases of gestosis, discovered immediately before parturition and associated with moderate albuminuria and raised blood pressure, 1 case of mild puerperal endometritis, 1 case of afebrile, acute cystitis, and 1 premature birth with the child weighing 1,300 gm.

The changes of the blood characteristics and the time of the examinations of this material appear in table 26. The variation is similar to that of the main material, and I have therefore only studied how the blood values have changed from the period about 6 weeks after delivery to the period some months later, and from there to about another month later. Between the last two periods the patients had been given about 10 gm. of iron (see above). In this analysis the differences were formed and tested on the null hypothesis with the *t*-test. Since only 43 differences could be formed at the first comparison (cf. table 26 and table 27) the differences do not agree, but this is unimportant.

From the period about 6 weeks after delivery to the period some months later hematocrit, hemoglobin and the corpuscular values containing hemoglobin have increased significantly, but the variation of the other blood characteristics may be due to random errors. Between the two last periods, i. e. during iron medication, the increase is signif-

Table 26. Mean blood values in different periods during and after pregnancy in 44 subjects followed throughout pregnancy and post partum. After blooddetermination some months post partum iron treatment with about 10 gm iron (ferrous fartrate). (Asterisked columns do not have the ordinary total: total must be computed separately in each case.)

Blood characteristics divided into classes according to Hb-value some months p.p.:

I = 8.35—9.87 gm. Hb/100 cc blood.

II = 9.87—11.39 gm. Hb/100 cc blood.

III = 11.39—12.91 gm. Hb/100 cc blood.

Blood characteristics	Hb class	No.	Pe. ₁ : About 11th w. of pregn. — range 6—21 w.	Pe. ₂ : About 35th w. of pregn. — range 30—37 w.	Pe. ₃ : About 7th day post partum — range 2—10 d. ¹	Pe. ₄ : About 6 w. post partum — range 3—10 w. ²	Pe. ₅ : Some months post partum (see table 25)	Pe. ₆ : After iron medication during about 30 d.
			M ± ε (M)	M ± ε (M)	M ± ε (M)	M ± ε (M)	M ± ε (M)	M ± ε (M)
Hemoglobin (gm/100 cc blood)	I	5	10.3	9.2	9.3	8.6	9.4	11.6
	II	17	10.7	9.6	10.0	9.9	10.9	12.0
	III	22	10.7	9.9	10.1 ³	10.4 ³	11.8	12.1
	Total	44	10.6 ± 0.11	9.7 ± 0.13	10.0 ± 0.12	10.0 ± 0.12	11.2 ± 0.13	12.0 ± 0.09
Red cells (mill./c.mm)	I	5	4.21	3.92	3.98	4.11	4.19	4.61
	II	17	3.94	3.82	4.02	4.07	3.99	4.32
	III	22	3.94	3.75	3.83 ³	4.05 ³	4.19	4.31
	Total	44	3.97 ± 0.05	3.80 ± 0.05	3.92 ± 0.05	4.06 ± 0.05	4.11 ± 0.04	4.35 ± 0.06
Hematocrit (vol. per cent)	I	5	36.8	32.4	31.9	33.1	32.5	38.8
	II	17	36.3	32.7	35.3	35.9	36.8	38.1
	III	22	36.6	33.7	34.8 ³	37.1 ³	38.9	38.8
	Total	44	36.5 ± 0.44	33.2 ± 0.45	34.6 ± 0.49	36.1 ± 0.34	37.3 ± 0.40	38.5 ± 0.33
M.C.H.C. (per cent)	I	5	28.6	28.6	28.8	26.1	26.9	29.9
	II	17	29.0	29.3	28.5	27.8	29.6	31.4
	III	22	29.2	29.5	29.1 ³	28.0 ³	30.4	31.2
	Total	44	29.1 ± 0.18	29.3 ± 0.22	28.8 ± 0.24	27.7 ± 0.21	29.7 ± 0.28	31.2 ± 0.17
M.C.H. (γγ)	I	5	25.0	23.5	23.1	20.8	21.9	25.2
	II	17	27.2	25.3	24.9	24.6	27.2	27.8
	III	22	27.3	26.4	26.4 ³	25.8 ³	28.2	28.2
	Total	44	27.0 ± 0.30	25.6 ± 0.30	25.4 ± 0.30	24.8 ± 0.42	27.1 ± 0.38	27.7 ± 0.28
M.C.V. (c.μ)	I	5	87.7	82.3	80.5	79.9	77.9	84.7
	II	17	93.9	85.9	87.6	88.9	92.0	88.6
	III	22	93.2	89.7	91.1 ³	92.0 ³	92.8	90.4
	Total	44	92.9 ± 1.00	87.4 ± 0.96	88.5 ± 1.18	89.4 ± 1.22	90.8 ± 1.08	89.0 ± 0.88
Serum iron (γ/100 cc)	I	5	120.0	60.0	73.0	58.0	59.0	(105.0)
	II	17	122.0	81.1	102.7 ⁵	86.4 ⁶	89.9	(124.7)
	III	22	132.0 ⁴	99.4 ³	87.7 ³	97.0 ³	102.5	(127.0) ³
	Total	44	126.5 ± 5.3	87.6 ± 4.9	91.4 ± 6.1	88.3 ± 5.3	92.7 ± 5.5	(123.5) ± 4.8

¹ (only in 4 cases less than 4 days). ² (in 35 cases 5—7 weeks.) ³ No. of cases = 21. ⁴ No. of cases = 20. ⁵ No. of cases = 15. ⁶ No. of cases = 16.

Table 27. Mean of the individual differences and *P* values between some of the periods in table 26. $D \pm \varepsilon(D)$ = difference $\pm$ standard error of the difference.

Blood characteristics	No.	$D \pm \varepsilon(D)$	P
Diff.: some months p.p. and about 6 w. p.p.			
Hemoglobin	43	1.1 $\pm$ 0.10	<0.001
Red cells	43	0.04 $\pm$ 0.052	>0.2
Hematocrit	43	1.2 $\pm$ 0.29	<0.001
M.C.H.C.	43	2.1 $\pm$ 0.30	<0.001
M.C.H.	43	2.4 $\pm$ 0.42	<0.001
M.C.V.	43	1.3 $\pm$ 1.17	>0.2
Serum iron	42	1.4 $\pm$ 5.9	>0.2
Diff.: after and before iron treatment			
Hemoglobin	44	0.9 $\pm$ 0.14	<0.001
Red cells	44	0.23 $\pm$ 0.056	<0.001
Hematocrit	44	1.2 $\pm$ 0.44	0.05—0.01 ¹
M.C.H.C.	44	1.5 $\pm$ 0.25	<0.001
M.C.H.	44	0.6 $\pm$ 0.30	$\approx$ 0.05
M.C.V.	44	-1.9 $\pm$ 0.96	$\approx$ 0.05

¹ close to 0.01.

icant for hemoglobin, red cells and the mean corpuscular hemoglobin concentration, but the other changes may be due to random errors (The hematocrit increase is almost probable.) True, the serum iron value has gone up 30.8 ± 7.3 γ per cent, but this increase must not be accorded undue importance, for these test persons might have taken iron 12—14 hours earlier.

It would have been desirable to compare the blood values after iron treatment with a similar material given no iron. There was no possibility of doing so and these values were therefore compared with my normal material. It appears that the blood values in these materials agree fairly well (serum iron doubtful), excepting the mean corpuscular volume, which lies 4.0 ± 1.0 c. μ . lower, and mean corpuscular hemoglobin, where the lowering is statistically probable being 1.0 ± 0.34 $\gamma\gamma$ ($0.01 > P > 0.001$) in the iron treated cases. (The difference for red cells is 0.15 ± 0.067 mill per c. mm. blood, $0.05 > P > 0.01$.)

I shall now compare the 3 above-mentioned classes during and after pregnancy; the results appear in table 28. The class variation of the different blood characteristics should be compared within periods, i. e. the period variation should be eliminated. Analysis of variance has therefore been used in the statistical treatment.

Table 28 contains only the most important results as it otherwise would have become too large.

Table 28. Comparison between the different hemoglobin classes of the periods according to table 26. (Class interval see table 12.)

Source of variation	Degrees of freedom	Mean square	P
<i>Hemoglobin</i>			
Within Pe. ₁ , Pe. ₂ and Pe. ₃	128		
Between Hb-classes	6	21.4	>0.2
Within Hb-classes	122	15.8	
Within Pe. ₄ and Pe. ₅	85		
Between Hb-classes	4	238.6	<0.001
Within Hb-classes	81	6.2	
<i>Red cells</i>			
Within all 6 periods	256		
Between Hb-classes	12	37.3	>0.2
Within Hb-classes	244	28.9	
<i>Hematocrit</i>			
Within Pe. ₁ , Pe. ₂ and Pe. ₃	128		
Between Hb-classes	6	38.4	>0.2
Within Hb-classes	122	36.7	
Within Pe. ₄ and Pe. ₅	85		
Between Hb-classes	4	239.9	<0.001
Within Hb-classes	81	13.4	
<i>Mean corpuscular hemoglobin-concentration</i>			
Within Pe. ₁ , Pe. ₂ , Pe. ₃ and Pe. ₄ ...	170		
Between Hb-classes	8	46.3	0.2—0.05
Within Hb-classes	162	31.2	
Within Pe. ₄ and Pe. ₅	85		
Between Hb-classes	4	262.9	<0.001
Within Hb-classes	81	32.7	
<i>Mean corpuscular hemoglobin</i>			
Within Pe. ₁ and Pe. ₂	86		
Between Hb-classes	4	240.2	0.01—0.001
Within Hb-classes	82	53.3	
Within Pe. ₂ , Pe. ₃ and Pe. ₄	127		
Between Hb-classes	6	509.6	<0.001
Within Hb-classes	121	59.4	
<i>Mean corpuscular volume</i>			
Within Pe. ₁ and Pe. ₂	86		
Between Hb-classes	4	111.2	0.05—0.01
Within Hb-classes	82	39.4	

(Table 28 continued.)

Source of variation	Degrees of freedom	Mean square	P
<i>Mean corpuscular volume</i> (Continued.)			
Within Pe. ₁ , Pe. ₂ and Pe. ₃	128		
Between Hb-classes	6	154.5	0.01—0.001
Within Hb-classes	122	43.3	
<i>Serum iron</i>			
Within all periods (excl. Pe. ₆)	207		
Between Hb-classes	10	106.5	0.05—0.01
Within Hb-classes	197	46.7	close to 0.01

The classes lie close together throughout pregnancy and in the period about one week after delivery for hemoglobin, hematocrit and mean corpuscular hemoglobin concentration. Later the classes disperse (for mean corpuscular hemoglobin concentration not until the period about 6 weeks after delivery), but under the action of the iron treatment they again come close together.

The red cell variation between the classes for the entire material may be due to random errors. Even during pregnancy the same mean corpuscular hemoglobin variation is probably significant, and later it increases still more. For mean corpuscular volume the variation during pregnancy may be due to random errors, but later it increases somewhat and can be considered probable. For the material in toto the variation between classes for mean corpuscular volume is significant. The same variation for serum iron does not quite attain statistical probability.

Summary and Discussion.

On the whole the blood characteristics in these 44 cases exhibit the same variation as in the main material. From about 6 weeks after to some months after delivery, and during the subsequent iron treatment, the values generally increase. The changes in this material of 44 cases as compared with the main material do not attain the same statistical significance and sometimes they do not even attain statistical probability. This is partly due to the number of cases and partly to the fact that I have not taken into account the intrapartum hemorrhage in statistically treating the 44 cases.

Although the material is small, the grouping in classes according to the hemoglobin value some months post partum has produced some valuable information, partly confirming what I have emphasized earlier, viz. that the blood changes during pregnancy affect the material uni-

formly: the classes into which the blood characteristics are divided generally lie close together during pregnancy and are not dispersed until after delivery.

This material of 44 cases shows that some months after delivery there still exists a significant hypochromic anemia of microcytic type in some of the patients, and that this anemia tends to respond well to iron treatment.

In the highest class, the blood values about 6 months after delivery (before iron therapy) are not very unlike those in the normal material. The serum iron value, however, is $24.3 \pm 7.2 \gamma$ per cent lower, a significant difference ($P \approx 0.001$). The mean blood values of all the 44 cases at this time lie significantly below the mean normal figures except for red cells and mean corpuscular volume.

I have previously pointed out that the changes in the blood values during the last 8 weeks of pregnancy may suggest a deficiency, most likely of iron, and that this deficiency might be accentuated by the intrapartum hemorrhage (cf. Chapters 5 and 6). How does this fit in with the facts?

At the examination some months after delivery, the lowest class contained the two largest hemorrhages of all the cases, but none of the other 3 had lost more than 400 cc of blood. These latter cases had already been examined 3 months after delivery. One of them had had more than one child before.

In the middle class, where the erythroid elements, hematocrit and serum iron values generally are fairly low, the mean intrapartum hemorrhage was lower than the mean hemorrhage in the highest class.

There are some differences as regards the time of the examination. In the highest class the patients were on the whole examined later than in the other two classes. The patients in the highest class therefore had more time to compensate the deficiency. (Approximately the same number of cases had previously been given iron in each class.) Here also, however, a slight iron deficiency may be surmised to remain because of the significantly lower serum iron value than in the normal material.

The blood values, thus, return to normal only slowly; on the basis of the present material the blood values will tend to lie higher the later the examination takes place after delivery.

This suggests that pregnancy and the intrapartum hemorrhage are followed by a deficient condition which takes a long time to remedy without special measures. The symptoms of anemia described in Chapters 5 and 6 are still fully evident some months after delivery with subnormal serum iron and in half the cases hypochromia. In 5 of the 44 cases the symptoms are pronounced and indicate hypochromic, microcytic anemia. The iron treatment proved effective.

In Chapter 5 it appeared that, during pregnancy, multiparae probably

show a lower serum iron value than women with 0—1 previous deliveries. This could be explained by the conditions described above, and may be a sign of smaller iron depots in these women.

CHAPTER 8.

Effect of Iron Administration in Pregnancy.

In Chapter 5 it was made clear that the erythroid elements and hematocrit level lie significantly lower than in the normal material up to the 16th week of pregnancy; then a statistically significant reduction follows. During the last 16 weeks the hemoglobin and hematocrit values do not change perceptibly, whereas the red cell count increases significantly and the mean corpuscular volume drops. Remaining on a normal level until about the 24th week of pregnancy, the serum iron value then decreases rapidly. Even in the 6th or 7th week of pregnancy marked hypochromia exists, and from then onwards until parturition the value for the mean corpuscular hemoglobin concentration is subject only to random variation. Other statistically demonstrable, correlative and regressive changes, too, set in at the end of pregnancy, and by this time the main material has evidently contracted a degree of microcytic hypochromia.

In Chapters 4 and 5, particularly, I have discussed anemia and its implications during pregnancy, pointing out that a reduction alone, although fairly marked, of the erythroid elements and the hematocrit value should not be called anemia unless there are additional symptoms. On the other hand, it would seem justifiable to label as anemia the changes taking place during the final 8-week period of pregnancy.

An anemic condition implies that there is a deficiency, and I have pointed out that the conditions obtaining, when this assumed deficiency occurs, suggest a lack of iron. This assumption is borne out by the slow postparturient regeneration of blood in conjunction with more pronounced hypochromia 6 weeks after delivery than during pregnancy. Moreover, many months after delivery there are often marked hypochromia and low serum iron.

I shall now describe to what extent the changes in the blood characteristics that occur towards the end of pregnancy can be prevented by administration of iron salts. I shall also compare the blood values about 6 weeks after delivery in a material so treated, with the corresponding values in the main material and the normal material, respectively. (A detailed statistical analysis of the latter comparisons is impossible, however, because of circumstances to be described.) Conceivably, the results of such analysis may illuminate the problem of iron deficiency as a reason for the anemization of pregnancy.

The material comprises 53 pregnant women aged 15—41. The selection was carried out along the same principles as for the main material, apart from the gestational phase. The age median is 25.5 years, the lower quartile lying at 22.6, the upper at 29.8 years. Only 3 persons were younger than 18 years.

These 53 persons were healthy all the time; some, who were initially included in the material but later developed signs of gestosis, have been excluded. At the first examination some subjects, to be sure, had rather low blood values, but they were not low enough to warrant the label anemia. In one case the mean corpuscular volume was 77 c. μ , the mean corpuscular hemoglobin concentration 25 per cent and the hemoglobin value 8.5 gm. per 100 cc blood. This case was not excluded from the material.

Table 29 shows that 25 cases were first examined in the 16th—24th week of pregnancy, and 28 in the 24th—32nd week. During pregnancy, 52 cases were reexamined after about 2 months while 22 were controlled

Table 29. *Mean blood values in different periods during pregnancy before and after iron treatment. In the group treated with iron from 3rd period, the average amount of iron (as ferrous tartrate) from 3rd to 5th period was 40 gm (range 12—60 gm), and from 3rd to 4th period in 19 cases (amount of iron uncertain in 5 cases) 22 gm., range 6—40 gm. The average amount of iron in the group treated from 4th period was 31 gm (range 20—52 gm).*

Blood characteristics	Periods of pregnancy				
	Pd ₃ = 16—24 weeks, Pd ₄ = 24—32 weeks, Pd ₅ = 32—40 weeks				
	Before iron treatment in Pd ₃ , average 20 w.	Pd ₄ . Treatment averaged 7 w., range 3—13 w., in 17 cases 5—10 w.	Pd ₅ . Treatment averaged 14 w., range 10—18 weeks	Before iron treatment in Pd ₄ , average 27 w.	Pd ₅ . Treatment averaged 10 w., range 4—15 w., in 24 cases 8—12 w.
	$M \pm \varepsilon (M)$	$M \pm \varepsilon (M)$	$M \pm \varepsilon (M)$	$M \pm \varepsilon (M)$	$M \pm \varepsilon (M)$
No. of cases	25	24	22	28	28
Hemoglobin (gm/100 cc blood)	10.5 $\pm$ 0.17	11.2 $\pm$ 0.12	11.8 $\pm$ 0.17	10.6 $\pm$ 0.14	12.0 $\pm$ 0.11
Red cells (mill./c.mm)	3.98 $\pm$ 0.053	4.10 $\pm$ 0.036	4.12 $\pm$ 0.049	4.01 $\pm$ 0.047 ¹	4.25 $\pm$ 0.047
Hematocrit (vol. per cent)	35.5 $\pm$ 0.41	36.7 $\pm$ 0.41	38.0 $\pm$ 0.40	35.5 $\pm$ 0.50	38.8 $\pm$ 0.44
M.C.H.C. (per cent)	29.8 $\pm$ 0.39	30.7 $\pm$ 0.28	31.0 $\pm$ 0.36	29.9 $\pm$ 0.35	31.1 $\pm$ 0.25
M.C.H. ($\gamma\gamma$)	26.6 $\pm$ 0.43	27.4 $\pm$ 0.27	28.6 $\pm$ 0.31	26.6 $\pm$ 0.28 ¹	28.3 $\pm$ 0.23
M.C.V. (c. μ)	89.4 $\pm$ 1.26	89.1 $\pm$ 0.82	92.4 $\pm$ 0.99	89.2 $\pm$ 1.02 ¹	91.2 $\pm$ 0.87
No. of cases	23	9	15	25	23
Serum iron (γ /100 cc)	99.0 $\pm$ 4.9	99.8 $\pm$ (4.9)	116.3 $\pm$ 4.4	99.4 $\pm$ 5.5	134.2 $\pm$ 5.9

¹ No. = 27.

after about 14 weeks. All but one of these 22 cases were examined 3 times during pregnancy, and the second examination took place about 7 weeks after the first. Of the 53 persons treated with iron 42 were reexamined about 6 weeks after parturition: none of them had been treated with iron salts in the meantime. It should be mentioned that some have been excluded who were examined before the 16th week of pregnancy. Only one set of figures has been used for test persons examined more than once in the same period, that set being chosen which was farthest from the initiation of treatment.

The perorally administered iron salt in tablet form was ferrous tartrate (proprietary name: Novofer forte).¹ Each tablet contains 90 mg. iron. The preparation was usually well tolerated. The amount of iron salt administered, expressed in gm of iron is seen in table 29. The iron quantity was very considerable in most cases, as I took pains to make it so and to protract the treatment.

The method is described in the Chapter on Methods. However, in estimating the number of red cells only 16 CD-squares were counted (each CD-square = $1/800$ c. mm.), or $16/800$ c. mm. Nor were double serum iron determinations made. Since, apart from serum iron, the determinations in this case were not carried out by the assistant who analyzed the main material, the error of method for the material treated with iron will be given. For hemoglobin it was just below 2 per cent, for red cells just below 2.5 per cent, and for hematocrit about 1.3 per cent. Yet another assistant carried out the determinations for the 42 subjects who were examined about 6 weeks after delivery. Here the error of method for hemoglobin was just below 2.5 per cent, for red cells rather more than 2 per cent, and for hematocrit rather more than 1.5 per cent. Mutually compared, the two assistants who analyzed the pregnant, iron-treated material obtained approximately the same values for hemoglobin and hematocrit, but the variation in the red cell count was comparatively large. Their hemoglobin and hematocrit readings differed negligibly from the corresponding values as determined by the assistant who had dealt with the main and the normal materials.

The author should like to emphasize that this iron-treated material consequently is not fully comparable with the main and the normal material, and this is especially true of the red cell count. The materials are equivalent, however, as regards the serum iron, since all the serum iron determinations were made by the same assistant: the main purpose is to study the effect of the iron treatment during different phases of pregnancy, and other comparisons are therefore of subordinate importance even if they do give some information. Table 29 shows the results of the investigation and table 30 the significance of the mean differences for the blood characteristics that were recorded during the treatment.

¹ The author is most indebted to AB Pharmacia, Stockholm, for gratuitously supplying the preparation.

Table 30. *Mean of the individual differences and P values between the different periods in table 29.* $D \pm \varepsilon(D)$ = difference $\pm$ standard error of the difference.

Blood characteristics	No.	$D \pm \varepsilon(D)$	P
Diff.: 24—32 weeks and 16—14 weeks			
Hemoglobin	24	0.7 ± 0.12	<0.001
Red cells	24	0.11 ± 0.064	≈ 0.1
Hematocrit	24	1.2 ± 0.38	$0.01-0.001$
M.C.H.C.	24	0.9 ± 0.35	$0.05-0.01^1$
M.C.H.	24	0.9 ± 0.45	$0.2-0.05$
M.C.V.	24	0.1 ± 1.50	>0.2
Serum iron	9	0.2 ± 10.4	>0.2
Diff.: 32—40 weeks and 16—24 weeks			
Hemoglobin	22	1.2 ± 0.23	<0.001
Red cells	22	0.15 ± 0.061	$0.05-0.01$
Hematocrit	22	2.3 ± 0.47	<0.001
M.C.H.C.	22	1.2 ± 0.54	$0.05-0.01$
M.C.H.	22	1.8 ± 0.46	≈ 0.001
M.C.V.	22	2.4 ± 1.36	$0.2-0.05$
Serum iron	14	20.4 ± 6.0	$0.01-0.001$
Diff.: 32—40 weeks and 24—32 weeks ³			
Hemoglobin	28	1.5 ± 0.18	<0.001
Red cells	27	0.24 ± 0.067	$0.01-0.001^2$
Hematocrit	28	3.2 ± 0.62	<0.001
M.C.H.C.	28	1.2 ± 0.43	≈ 0.01
M.C.H.	27	1.7 ± 0.36	<0.001
M.C.V.	27	2.1 ± 1.27	$0.2-0.05$
Serum iron	20	35.9 ± 5.4	<0.001

¹ close to 0.01.² close to 0.001.³ (treated with iron only from weeks 24—32).

In the statistical treatment, the differences were formed (cf. p. 40). The differences according to table 29 do not always agree with those in table 30, because the number of cases in the periods, and consequently the differences, are not always the same. This is, evidently, unimportant.

The blood values in the subjects treated from the 16th—24th week of pregnancy (3rd period) to the 24th—32nd week of pregnancy (4th period) did not increase either probably or significantly, except as regards hemoglobin and hematocrit for which the differences are respectively significant and probable. The increased mean corpuscular hemoglobin concentration is almost probable.

The blood values for the 3rd compared with the 5th period (32nd

—40th week) shows significant increases for hemoglobin, hematocrit and mean corpuscular hemoglobin. The serum iron increase is probable. The increase of the other blood characteristics may be a result of random variation.

In the 28 instances when the iron treatment was initiated in the 4th period (week 24—32), the increase is significant for erythroid elements, hematocrit value, serum iron, and mean corpuscular hemoglobin. The increase in the mean corpuscular hemoglobin concentration is statistically probable, but the raised mean corpuscular volume may be nothing but random variation.

The blood characteristics of 42 of the subjects treated with iron salt during pregnancy were determined about 6 weeks after delivery. The variability expressed in weeks post partum was 4—9 weeks and in 29 cases 5—7 weeks. These 42 persons were not given iron salts after delivery.

Table 31 shows the postparturient blood values in these 42 cases. They are grouped in the same hemorrhage classes as the main material according to the loss of blood at delivery. In 12 cases it was 0—300 cc, in 21 cases 300—600 cc and in 9 cases more than 600 cc. In 5 of these 9 cases the hemorrhage exceeded 900 cc, the maximum loss of blood being 1,100 cc. The median for the hemorrhage lies at 370 cc.

The differences, according to table 31, between hemorrhage classes may be due to random variation for all the blood characteristics at the period about 6 weeks post partum. However, if the material is grouped in 4 hemorrhage classes according to table 21, p. 54, the differences become statistically probable for the erythroid elements and hematocrit, the lowest values lying in the group with the greatest intrapartum hemorrhage. But this group contains only a small number of cases, 5 subjects, and therefore the influence of the intrapartum hemorrhage

Table 31. *Mean blood values of 42 subjects about 6 weeks post partum, treated during pregnancy with iron.*

Blood characteristics	Heemorrhage at the delivery in cc.			
	0—300	300—600	600—	Total $M \pm \epsilon (M)$
<i>No. of cases</i>	13	20	9	42
Hemoglobin (gm/100 cc blood) ..	12.3	12.6	11.6	12.3 ± 0.15
Red cells (mill./c.mm)	4.46	4.61	4.34	4.51 ± 0.05
Hematocrit (vol. per cent)	39.3	40.3	37.1	39.3 ± 0.47
M.C.H.C. (per cent)	31.5	31.3	31.3	31.3 ± 0.26
M.C.H. ($\gamma\gamma$)	27.7	27.3	26.7	27.3 ± 0.26
M.C.V. (c. μ)	88.5	87.6	85.3	87.4 ± 1.0
<i>No. of cases</i>	10	9	8	27
Serum iron (γ /100 cc)	162.0	147.6	127.6	147.0 ± 8.8

on the blood characteristics about 6 weeks post partum is not definitely ascertainable.

With the emphatic reservation that, apart from serum iron, the following suffers from certain errors (probably as regards red cell count especially), a comparison will be made partly between the 5th period of pregnancy and about 6 weeks post partum in the gravid material treated with iron, and partly between these periods on the one hand, and the main material and the normal material on the other.

1. The 5th period of pregnancy (50 cases) compared with about 6 weeks post partum (42 cases) in the gravid material treated with iron shows discrepancies, possibly the result of random variation in the values for hemoglobin, hematocrit, mean corpuscular hemoglobin concentration, and serum iron. The red cell count has increased significantly (0.31 ± 0.06) to the period post partum while the corpuscular values dependent on it have dropped significantly (M.C.H.C. 1.12 ± 0.32 and M.C.V. 4.37 ± 1.19).

2. A comparison between the iron-treated material (42 cases) and the main material (101 cases) about 6 weeks post partum shows differences that may be random for the mean corpuscular volume. Other blood characteristics are lower in the main material. (Thus the difference $\pm$ standard error = 1.6 ± 0.19 gm per 100 cc blood for hemoglobin, 0.36 ± 0.07 mill. per c. mm blood for red cells, 1.8 ± 0.58 vol. per cent for hematocrit, 1.7 ± 0.38 $\gamma\gamma$ for M.C.H., and 51.8 ± 9.4 γ per cent for serum iron.)

3. The normal material compared with the 5th. period of the iron-treated material shows small, possibly random, variations.

4. A comparison between the period about 6 weeks post partum in the iron-treated material and the normal material shows differences which may be random for all blood characteristics except red cells and its dependent corpuscular values. The red cell count lies significantly lower in the normal material (0.31 ± 0.059), whereas M.C.H. lies higher (1.1 ± 0.31) as does M.C.V. (5.63 ± 1.13).

A summary of the above, at first neglecting the red blood cells and their dependent corpuscular values, yields the following results:

- a. the differences in blood values in the iron-treated material between the 5th. period of pregnancy and about 6 weeks after delivery are such that they may be only the result of random variation,
- b. there are considerable differences, especially in the values for hemoglobin, mean corpuscular hemoglobin concentration, and serum iron about 6 weeks after delivery, between the iron-treated material and the main material which has the lower values,
- c. the differences in blood characteristics between the iron-treated material and the normal material both in the 5th period of pregnancy and about 6 weeks after delivery are negligible.

For reasons of method described in this chapter it is probable that these results may be reliable. The interpretation of the variation in the red cell count is more doubtful. Although I have given the appropriate figures I do not consider myself justified in drawing any conclusions from them, and I therefore leave the question open.

Summary and Discussion.

In the Review of Literature I discuss the results arrived at by other investigators who have treated pregnant women with iron preparations. The objections that have been raised against the efficacy of iron treatment in pregnancy, viz., that irrespective of the medication

the blood values will increase towards the end of pregnancy (Dieckmann *et al.*) and that the plasma volume decreases at term (Oberst and Plass) are shown by my findings to be doubtful. The changes occurring in the main material undoubtedly suggest a uniform anemizing process which, however, may conceal a reduction in the amount of plasma towards the end of pregnancy. The reasons why iron medication during pregnancy has given discrepant or unreliable results may be that the treated material often was small, the duration of treatment often too short, the stage of pregnancy not fixed, and possibly that the iron dosage per unit of time was inadequate.

Turning now to my results of the iron treatment with massive dosage and protracted medication, we shall find the following (see tables 29 and 30): when the treatment was initiated in the 16th—24th week of pregnancy (3rd period) the erythroid elements had not decreased in the 24th—32nd week (4th period) as in the main material. Only hemoglobin increases significantly and the rise corresponds to the relative hemoglobin deficiency I assume occurs during pregnancy. The hematocrit increase is probable. Here the iron possibly has a promoting effect on the synthesis of hemoglobin without there being any sound reason to suspect iron deficiency in the woman at this stage of pregnancy. (Also in non-pregnant healthy women Widdowson and McCance (1936) and Vahlquist (1941), among others, have obtained a significant increase with the aid of iron treatment.)

From the 3rd period (16th—24th week of pregnancy) to the 5th period (32nd—40th week) in the first group and from the 4th period (24th—32nd week) to the 5th period in the second group (see table 30) the hemoglobin and hematocrit values increase considerably. In the second group the red cell count also increases significantly. The mean corpuscular hemoglobin increases significantly in both groups, while the mean corpuscular hemoglobin concentration shows a statistically probable increase in the second group. The changes affecting the mean corpuscular volume are statistically random. The increase in the serum iron value during the treatment is certainly real. In this material, consisting of iron-treated pregnant women, we consequently get a change in the blood values quite different from that in the main material. Instead of the symptoms of anemia demonstrated by the main material at the end of pregnancy, viz. low blood values including low serum iron value and decreasing mean corpuscular volume, we here find raised blood values without reduction of the mean corpuscular volume.

Because of the administration of iron salt (in this case a bivalent, soluble, organic iron compound), the relatively mild but definite anemia occurring at the end of pregnancy can be prevented, and in this iron-treated material the blood characteristics in the 5th period of pregnancy will approximate the blood values in the normal material.

Yet another strong point in favour of the efficacy of the treatment

is afforded by the blood characteristics about 6 weeks after delivery in 42 of the women treated with iron during their pregnancy. Although all the hemorrhage classes have been consolidated into one, the means differ only negligibly from the normal material apart for the red cells and their dependent corpuscular values. (Earlier in this chapter I have discussed at length the importance of these differences and stated why they should not be accorded excessive attention.) The blood characteristics about 6 weeks after delivery in the iron-treated material also lie substantially higher than the corresponding values in the main material. (As regards red corpuscles see above.)

It is therefore likely that the reason for the anemic condition at the end of pregnancy is iron deficiency and, accordingly, it would be interesting to estimate the approximate loss of iron during this period despite the fact that the following problems have been debated time and again by other authors. The loss of iron during pregnancy, parturition and lactation has been variously estimated, but the difference between this loss and the total menstrual loss during an equal period is probably not very great. Pregnancy and delivery might on the other hand cause a greater iron loss per unit of time. Naturally, every estimation of such losses cannot be anything but very rough approximations, but since the figures available nevertheless are in fairly good agreement a computation might be of some value.

In the main material the iron requirements during pregnancy and delivery would seem to be about 700 mg., of which about 600 mg. is reserved for fetus, placenta and uterus and a mean of rather more than 100 mg. is lost in the intrapartum hemorrhage. (Cf. Review of Literature for other figures.) If one menstrual period is equivalent to a loss of about 25 mg. of iron, the iron loss in connection with pregnancy and delivery would therefore considerably exceed the total menstrual loss for an equal period.

As yet we have no means of estimating quantitatively the importance of the depot iron for human hematopoiesis, but on the basis of animal experiments it is justifiable to assume that a reduction can result in reduced erythropoiesis. It is admittedly probable that perorally administered iron preparations are more easily absorbed during pregnancy, at least in its later phase, but this says nothing about the absorption of iron contained in the food. If this absorption is not greater than usual, sideropenia could very well be the result. The frequently reported and common hypochylia and achylia during pregnancy may naturally imply a reduced availability of the iron in the food, resulting in decreased absorption.

The endocrine balance during pregnancy undergoes great changes. The variation of some of the blood values may of course be due to this circumstance, even if direct proofs of such an interpretation in human beings are lacking. The anemic changes in the main material

towards the end of pregnancy, however, must, according to the above, most likely be regarded as a deficient condition.

The practical conclusion to be drawn from the discussion is that the regular onset of anemia during the last phase of pregnancy can be prevented by a sufficiently prolonged and intensive administration of a suitable iron salt. On the basis of the experiments made in this investigation the author cannot with certainty give any detailed instructions for such medication. Administration of an iron salt, like the one used in the experiments, during the last two months of pregnancy gives fully satisfactory results.

Summary.

In the last two or three decades a very profuse literature has been published, dealing with the characteristics of the blood during and after pregnancy and the causes for their changes. It has been demonstrated that the hemoglobin content, red cell count, and hematocrit value decrease in pregnancy, and afterwards gradually return to their normal levels. Precisely when this takes place, and the interrelationship between these blood elements has not been elucidated. The investigations dealing with serum iron have not fully clarified how it changes in pregnancy and puerperium, although it has been postulated that the value decreases in the latter half of pregnancy and increases post partum.

Hematologic studies demand extremely accurate methods. Therefore I have consistently made double determinations (except of serum iron in a small number of instances) and used standardized apparatus. I have also made use of Enghoff's results of 1937 concerning hematologic technique.

In my investigation the standard error of measurement is: for hemoglobin not quite 1.5 per cent, for red blood cells about 2.8 per cent, for hematocrit rather more than 1 per cent, and for serum iron about 4 per cent. One and the same assistant has carried out most of the determinations. Only as regards the subjects treated with iron during pregnancy the determinations were made by other assistants. Their standard errors of measurement do not appreciably differ from the above values.

The main material comprises 136 healthy women who were followed during pregnancy up to about 6 weeks post partum. All of them were examined for the first time before the 24th week and 130 of them before the 20th week. Chapter 3 contains a detailed description of the material. A second material consisting of pregnant women treated with perorally administered iron salts is described. (See Chapter 8.)

The mean blood values for 98 healthy, nulliparous women with about the same age distribution as the main pregnant material are also given. (See Chapter 4.) I have emphasized the importance of relating the changes in the blood values to a normal material of one's own, at least for the present purposes. I have also discussed the concept of anemia with special reference to the definition of anemia during pregnancy. (See Chapter 4.)

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In my material the statistical analysis of the blood changes in pregnancy has given the following results (Chapter 5):

1. Even before the end of the 16th week, hemoglobin, red cell, and hematocrit mean values as well as mean corpuscular hemoglobin and mean corpuscular hemoglobin concentration lie significantly lower than in the normal material.

After weeks 8—16, the hemoglobin, red cell, and hematocrit values show a further marked decrease up to weeks 24—32. From then onwards until full term they remain fairly constant, except the red cell count which increases significantly.

2. The serum iron level is normal until weeks 16—24, but then it decreases markedly.

3. In weeks 6—7 the mean corpuscular hemoglobin concentration is significantly lower than in the normal material, but after that (with regard to the size of the material) the changes may be the result of random variation. After weeks 24—32, the mean corpuscular hemoglobin decreases still more and the mean corpuscular volume, having so far remained on a normal level, drops significantly.

4. In weeks 32—40, the means for all the studied blood characteristics lie significantly lower than in the normal material: hemoglobin about 18 per cent, red cells about 9 per cent, hematocrit about 13 per cent, and serum iron approximately 35 per cent. In this period the mean corpuscular hemoglobin concentration is about 5 per cent, the mean corpuscular hemoglobin about 10 per cent, and the mean corpuscular volume about 5 per cent lower than in the normal material.

5. The correlations between hemoglobin on the one hand and the mean corpuscular hemoglobin concentration and hematocrit on the other, and between hematocrit and mean corpuscular volume are much higher in the main material during the last 8 weeks of pregnancy than in the normal material. The coefficient of correlation between hemoglobin and mean corpuscular hemoglobin concentration is 0.92 ± 0.01 and between hemoglobin and hematocrit 0.86 ± 0.02 in the pregnant material during this period. Between the normal material and the main material during the first 4 periods of 8 weeks the coefficients of regression for mean corpuscular hemoglobin concentration on hemoglobin show differences that may be due to random variation. How-

ever, during the last 8 weeks ante partum the slope of the regression line changes significantly and becomes steeper.

6. During the entire period of pregnancy studied, i.e. as from weeks 6—7, there exists marked hypochromia according to item 3. The reason for this is uncertain. During the last 8 weeks before delivery this hypochromia is associated with microcytosis as well as other changes according to item 5. The blood values also are as a rule lowest at this time, although there is no appreciable difference as regards hemoglobin and hematocrit between this period and the preceding period of 8 weeks. Up to the last 8-week period of pregnancy the changes, apart from the hypochromia, may conceivably be attributed to dilution of the blood. During these last 8 weeks, however, the changes must have another cause: the material has uniformly moved towards anemia and the reason for the alteration probably is a deficiency, most likely of iron.

7. The serum iron level in the first half of pregnancy may suggest increased mobilization of iron. The decrease in the latter part of pregnancy may be caused by a deficiency or an increased consumption, or both.

8. The uniform change of the material during weeks 32—40 might be due to sideropenia preexisting to pregnancy. This does not seem to be the case, however. Everything indicates that the material did not come from a population with either active or latent anemia.

9. On this material, analysis of variance has yielded no differences between groups of different economic status. Perhaps this result could be expected, there being no appreciable differences in dietic habits between the groups.

With the limit put at 34 years of age, no influence of age could be discerned in the material, but the number of subjects in the older group was very small.

The material was also classified according to number of earlier deliveries. No important differences could be found except for serum iron. In the first three 8-week periods of pregnancy, the serum iron value in women who previously had given birth to more than one child was significantly lower than in women with a lower number of deliveries.

*

The analyses of the changes in the blood values during labour and in the puerperium have yielded the following results (Chapter 6):

a. The volume of the intrapartum hemorrhage strongly affects the hemoglobin, red blood cell, hematocrit, and serum iron levels. As is to be expected, the greater the hemorrhage, the lower will be the blood values. The volume of the intrapartum hemorrhage does not seem to affect the corpuscular values.

b. The values for hemoglobin, red cells and hematocrit increase

significantly from the last 10-week period of pregnancy until about 1 week after delivery, provided subjects with an intrapartum hemorrhage exceeding 600 cc are excluded. Between 1 and 6 weeks post partum these blood values remain fairly stable.

c. The combined serum iron value for the day of delivery and the day after exceeds the corresponding value for weeks 30—40 of pregnancy by a statistically significant margin. If consideration is given only to cases with an intrapartum hemorrhage less than 300 cc, there will first be a decrease with a subsequent significant increase about 1 week post partum. About 6 weeks after delivery the serum iron value is much the same in the latter hemorrhage group.

d. After delivery the mean corpuscular hemoglobin concentration decreases significantly. After about 1 week, this decrease is evident and it will be even more accentuated after about 6 weeks post partum. About 6 weeks post partum the mean corpuscular hemoglobin is still practically unchanged. The change of mean corpuscular volume can be due to random variation.

e. About 6 weeks post partum, the values for hemoglobin, mean corpuscular hemoglobin concentration, and mean corpuscular hemoglobin still lie significantly lower than the corresponding values in the normal material, even if subjects with intrapartum hemorrhages above 300 cc are disregarded.

f. The rapid increase of the blood values after delivery may indicate that the plasma volume quickly decreases.

g. The fact that 6 weeks after delivery the hypochromia is still more pronounced than during pregnancy shows that the regeneration of blood, and particularly the synthesis of hemoglobin, is slow.

*

In Chapter 7 the blood values of 44 subjects examined at least 3 months after delivery are reviewed. As long as 6 months post partum about half the cases are plainly hypochromic, and in most of the cases the serum iron value is subnormal. These symptoms are particularly pronounced in 5 of the subjects, so that it is justified to speak of hypochromic, microcytic anemia. The material is not large enough to permit definite conclusions but it seems as though, in addition to the intrapartum hemorrhage, the level of the blood values depends on the time that has elapsed from the delivery to the examination.

The results in Chapter 7 still more emphasize that pregnancy and delivery are associated with a deficient condition which it takes a long time to remedy. Iron salts have a curative effect on this condition.

*

Iron treatment during pregnancy with large doses administered by the peroral route gives the following results (Chapter 8):

α. If the treatment commences in week 16—24 and continues for about 7 weeks, a material of 24 subjects shows a significant increase of hemoglobin only. It is possible, however, that a larger material may yield significant differences for the other blood values also.

In 22 cases with the treatment initiated in weeks 16—24, and in 28 with the treatment initiated in weeks 24—32, all the blood characteristics (both groups taken as a whole), except mean corpuscular volume, have increased significantly after 14 and 10 weeks respectively. (The increase for mean corpuscular hemoglobin concentration is only probable.) Here the blood characteristics at term on the whole seem to agree with those of the normal material. (Some reservations are, however, discussed.)

β. 42 of the subjects were reexamined about 6 weeks post partum. At this time also the deviations from the normal material are insignificant, except for red blood cells and the dependent corpuscular values. (The reason for this is discussed; the deviation may be due to different techniques.)

γ. A sufficiently prolonged and intensive dosage of iron in the latter stages of pregnancy may prevent the symptoms of deficiency that arise in the main material, which was not given iron treatment. About 6 weeks post partum the blood values are normal or close to normal.

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